FORM PTO-1390 (REV 10-95) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. §371

ATTORNEY'S DOCKET NUMBER: SCH 1677

U.S. APPLICATION NO. (If known, see 37 CFR §1.5): 09/869000

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP99/10355	23 DECEMBER 1999	23 DECEMBER 1998

TITLE OF INVENTION

NEW 7-ALPHA, 17-ALPHA-BIS-ALKYLATED TESTOSTERONE DERIVATIVES AND THEIR USE IN LONG-TERM THERAPY OF ANDROGEN-DEPENDENT DISEASES

APPLICANT(S) FOR DO/EO/US

CLEVE, Arwed, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ■ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. §371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. §371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. §371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. §371(b) and PCT Articles 22 and 39(1).
4. ■ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ■ A copy of the International Application as filed (35 U.S.C. §371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ■ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ■ A translation of the International Application into English (35 U.S.C. §371(c)(2)).
7. ■ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. §371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ■ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. §371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. §371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. §371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 C.F.R. §§1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. §§3.28 and 3.31 is included.
13. ■ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/869000	PCT/EP99/10355	SCH 1677

17. ☒ The following fees are submitted:

		CALCULATIONS PTO USE ONLY
BASIC NATIONAL FEE (37 CFR §1.492 (a) (1) - (5)):		
Search Report has been prepared by the EPO or JPO	$860.00	
International preliminary examination fee paid to USPTO (37 CFR §1.482)	$690.00	
No international preliminary examination fee paid to USPTO (37 CFR §1.482) but international search fee paid to USPTO (37 CFR §1.445(a)(2))	$710.00	
Neither international preliminary examination fee (37 CFR §1.482) nor international search fee (37 CFR §1.445(a)(2)) paid to USPTO	$1000.00	
International preliminary examination fee paid to USPTO (37 CFR §1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)	$100.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =		$860.00
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 C.F.R. §1.492(e)).		

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	13 - 20 =	0	x $ 18.00	$0.00	
Independent claims	2 - 3 =	0	x $ 80.00	$0.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $ 270.00		
☐ **TOTAL OF ABOVE CALCULATIONS =**				$860.00	
Reduction of 1/2 for filing by small entity, if applicable. A Verified Small Entity Statement must also be filed (Note 37 C.F.R. §§1.9, 1.27, 1.28).					
☐ **SUBTOTAL =**				$860.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 C.F.R. §1.492(f)).					
☐ **TOTAL NATIONAL FEE =**				$860.00	
Fee for recording the enclosed assignment (37 C.F.R. §1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 C.F.R. §§3.28, 3.31). $40.00 per property.					
☐ **TOTAL FEES ENCLOSED =**				$860.00	
☐				Amount to be refunded:	
☐				charged:	

a. ■ A check in the amount of $860.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 13-3402 in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ■ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 13-3402. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 C.F.R. §§1.494 or 1.495 has not been met, a petition to revive (37 C.F.R. §1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO: Customer Number 23,599

PATENT TRADEMARK OFFICE

23599

Filed: 22 JUNE 2001

AJZ:jmm

SIGNATURE

Anthony J. Zelano

NAME

27,969

REGISTRATION NUMBER

IN THE UNITED STATES DESIGNATED/ELECTED OFFICE

International Application No.	:	PCT/EP99/10355
International Filing Date	:	23 DECEMBER 1999
Priority Date(s) Claimed	:	23 DECEMBER 1998
Applicant(s) (DO/EO/US)	:	CLEVE, Arwed, et al.

Title: NEW 7-ALPHA, 17-ALPHA-BIS-ALKYLATED TESTOSTERONE DERIVATIVES AND THEIR USE IN LONG-TERM THERAPY OF ANDROGEN-DEPENDENT DISEASES

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

SIR:

Prior to calculating the national fee, and prior to examination in the National Phase of the above-identified International application, please amend as follows:

IN THE CLAIMS:

3. (Amended) Testosterone derivatives according to claim 1, wherein R^{17b} is the hydroxy group, a C_1-C_5 alkoxy group or a C_1-C_3 alkanoyloxy group.

5. (Amended) Testosterone derivatives according to claim 1, wherein R^6 represents a hydrogen atom, the hydroxy group or a halogen atom.

6. (Amended) Testosterone derivatives according to claim 1, wherein R^{15} and R^{16} each represent a hydrogen atom.

7. (Amended) Testosterone derivatives according to claim 1, wherein radical ABCD means 9-hydroxynonyl, 7-(acetylsulfanyl)heptyl or 7-(4-cyanobutoxy)heptyl.

8. (Amended) Testosterone derivatives according to claim 1, wherein the five-ring- or six-ring-heteroaromatic compounds of radical C are pyrrole, thiophene, imidazole, thiazole, oxazole, triazole, thiadiazole, indole, benzoxazole, benzothiazole, pyridine, or pyrimidine.

9. (Amended) Testosterone derivatives according to claim 1, wherein they represent the following compounds:

7α-(9-Chlorononyl)-17α-methyl-3-oxoandrost-4-en-17β-yl-acetate

7α-(9-Chlorononyl)-17β-hydroxy-17α-methylandrost-4-en-3-one

17β-Hydroxy-7α-(9-iodononyl)-17α-methylandrost-4-en-3-one

17β-Hydroxy-7α-(9-hydroxynonyl)-17α-methylandrost-4-en-3-one

7α-(10-Chlorodecyl)-17β-hydroxy-17α-methylandrost-4-en-3-one

17β-Hydroxy-7α-(11-hydroxyundecyl)-17α-methylandrost-4-en-3-one

7α-(11-Bromoundecyl)-17β-hydroxy-17α-methylandrost-4-en-3-one

17β-Hydroxy-17α-methyl-7α-[7-(phenylsulfanyl)heptyl]androst-4-en-3-one

17β-Hydroxy-17α-methyl-7α-[9-[(4,4,5,5,5-pentafluoropentyl)sulfanyl]nonyl]androst-4-en-3-one

17β-Hydroxy-17α-methyl-7α-[9-(phenylsulfanyl)nonyl]androst-4-en-3-one

7α-[9-[(5-Chloropentyl)sulfanyl]nonyl]-17β-hydroxy-17α-methylandrost-4-en-3-one

17β-Hydroxy-7α-[9-[(5-hydroxypentyl)sulfanyl]nonyl]-17α-methylandrost-4-en-3-one

7α-(9-Azidononyl)-17β-hydroxy-17α-methylandrost-4-en-3-one

7α-[7-(Acetylsulfanyl)heptyl]-17β-hydroxy-17α-methylandrost-4-en-3-one

17β-Hydroxy-17α-methyl-7α-[7-[(4,4,5,5,5-pentafluoropentyl)sulfanyl]heptyl]androst-4-en-3-one

N-[7-(17β-Hydroxy-17α-methyl-3-oxoandrost-4-en-7α-yl)heptyl]pentanamide

17β-Hydroxy-17α-methyl-3-oxoandrost-4-en-7α-octane nitrile

5-[[7-(17β-Hydroxy-17α-methyl-3-oxoandrost-4-en-7α-yl)heptyl]oxy]pentanenitrile

17β-Hydroxy-17α-methyl-7α-[9-[(4,4,5,5,5-pentafluoropentyl)sulfinyl]nonyl]androst-4-en-3-one

N-[9-(17β-Hydroxy-17α-methyl-3-oxoandrost-4-en-7α-yl)nonyl]methanesulfonamide

7α-(9-Chlorononyl)-6β-hydroxy-17α-methyl-3-oxoandrost-4-en-17β-yl-acetate

12. (Amended) Use according to claim 10, wherein the testosterone derivatives of general formula I are used.

13. (Amended) Pharmaceutical agents that contain at least one testosterone derivative of general formula I according to claim 1 and physiologically compatible adjuvants and/or vehicles that are commonly used in galenicals.

REMARKS

The purpose of this Preliminary Amendment is to eliminate multiple dependent claims in order to avoid the additional fee. Applicants reserve the right to reintroduce claims to canceled combined subject matter.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 3, 5-9 and 12-13 have been amended as follows:

3. <u>(Amended)</u> Testosterone derivatives according to claim 1 ~~or 2~~, wherein R^{17b} is the hydroxy group, a C_1-C_5 alkoxy group or a C_1-C_3 alkanoyloxy group.

5. <u>(Amended)</u> Testosterone derivatives according to ~~one of~~ claims 1 ~~to 4~~, wherein R^6 represents a hydrogen atom, the hydroxy group or a halogen atom.

6. <u>(Amended)</u> Testosterone derivatives according to ~~one of~~ claim~~s~~ 1 ~~to 5~~, wherein R^{15} and R^{16} each represent a hydrogen atom.

7. <u>(Amended)</u> Testosterone derivatives according to ~~one of~~ claim~~s~~ 1 ~~to 6~~, wherein radical ABCD means 9-hydroxynonyl, 7-(acetylsulfanyl)heptyl or 7-(4-cyanobutoxy)heptyl.

8. <u>(Amended)</u> Testosterone derivatives according to ~~one of~~ claim~~s~~ 1 ~~to 6~~, wherein the five-ring- or six-ring-heteroaromatic compounds of radical C are pyrrole, thiophene, imidazole, thiazole, oxazole, triazole, thiadiazole, indole, benzoxazole, benzothiazole, pyridine, or pyrimidine.

9. <u>(Amended)</u> Testosterone derivatives according to ~~one of~~ claim~~s~~ 1 ~~to 8~~, wherein they represent the following compounds:

7α-(9-Chlorononyl)-17α-methyl-3-oxoandrost-4-en-17β-yl-acetate
7α-(9-Chlorononyl)-17β-hydroxy-17α-methylandrost-4-en-3-one
17β-Hydroxy-7α-(9-iodononyl)-17α-methylandrost-4-en-3-one
17β-Hydroxy-7α-(9-hydroxynonyl)-17α-methylandrost-4-en-3-one
7α-(10-Chlorodecyl)-17β-hydroxy-17α-methylandrost-4-en-3-one
17β-Hydroxy-7α-(11-hydroxyundecyl)-17α-methylandrost-4-en-3-one
7α-(11-Bromoundecyl)-17β-hydroxy-17α-methylandrost-4-en-3-one
17β-Hydroxy-17α-methyl-7α-[7-(phenylsulfanyl)heptyl]androst-4-en-3-one

17β-Hydroxy-17α-methyl-7α-[9-[(4,4,5,5,5-pentafluoropentyl)sulfanyl]nonyl]androst-4-en-3-one

17β-Hydroxy-17α-methyl-7α-[9-(phenylsulfanyl)nonyl]androst-4-en-3-one

7α-[9-[(5-Chloropentyl)sulfanyl]nonyl]-17β-hydroxy-17α-methylandrost-4-en-3-one

17β-Hydroxy-7α-[9-[(5-hydroxypentyl)sulfanyl]nonyl]-17α-methylandrost-4-en-3-one

7α-(9-Azidononyl)-17β-hydroxy-17α-methylandrost-4-en-3-one

7α-[7-(Acetylsulfanyl)heptyl]-17β-hydroxy-17α-methylandrost-4-en-3-one

17β-Hydroxy-17α-methyl-7α-[7-[(4,4,5,5,5-pentafluoropentyl)sulfanyl]heptyl]androst-4-en-3-one

N-[7-(17β-Hydroxy-17α-methyl-3-oxoandrost-4-en-7α-yl)heptyl]pentanamide

17β-Hydroxy-17α-methyl-3-oxoandrost-4-en-7α-octane nitrile

5-[[7-(17β-Hydroxy-17α-methyl-3-oxoandrost-4-en-7α-yl)heptyl]oxy]pentanenitrile

17β-Hydroxy-17α-methyl-7α-[9-[(4,4,5,5,5-pentafluoropentyl)sulfinyl]nonyl]androst-4-en-3-one

N-[9-(17β-Hydroxy-17α-methyl-3-oxoandrost-4-en-7α-yl)nonyl]methanesulfonamide

7α-(9-Chlorononyl)-6β-hydroxy-17α-methyl-3-oxoandrost-4-en-17β-yl-acetate

12. (Amended) Use according to claim 10 ~~or 11~~, wherein the testosterone derivatives ~~that are described in more detail in Claims 2 to 9~~ of general formula I are used.

13. (Amended) Pharmaceutical agents that contain at least one testosterone derivative of general formula I according to claims 1 ~~to 9~~ and physiologically compatible adjuvants and/or vehicles that are commonly used in galenicals.

NEW 7-ALPHA, 17-ALPHA-BIS-ALKYLATED TESTOSTERONE DERIVATIVES AND THEIR USE FOR LONG-TERM THERAPY FOR ANDROGEN-DEPENDENT DISEASES

This invention relates to new 7α, 17α, 17ß-substituted testosterone derivatives of general formula I and their use as pure antiandrogens for long-term therapy for androgen-dependent diseases, especially for long-term antiandrogen therapy for prostate cancer.

Current therapies of androgen-dependent diseases are based on the reduction or as complete as possible elimination of androgen-induced effects. This can be done by blocking the domains of androgen receptor (AR), to which the androgens bind as ligands, or by reduction of the available amount of androgens themselves (ligand depletion). In prostate cancer treatment, "ligand depletion" means a reduction of the serum testosterone level of testicular origin, which is to be achieved either with use of orchidectomy (removal of a testicle) or by hormone treatment with LHRH analogs or estrogens in high doses. This therapy for inhibiting androgen synthesis and/or reducing androgen concentration is effective only to a limited extent, however, since it has been noted in the meantime that even in the case of total absence of an androgen, non-blocked androgen

receptors can be biologically active (ligand-independent AR activation).

As an alternative or as an amendment to "ligand depletion," the antiandrogen therapy is used, which is based on the antagonistic blocking of the androgen receptor by so-called "antiandrogens" (nonsteroidal or steroidal compounds). Known antiandrogens, which are already used in clinical practice for prostate cancer treatment, are CPA (Schering AG), flutamide (Schering Plough), Casodex (Zeneca) and Anandron(R) (Roussel).

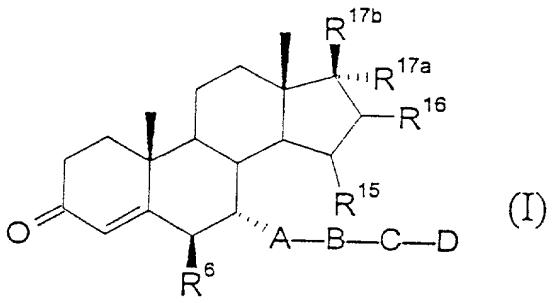
Although 80% of patients first respond to the above-mentioned therapies, almost all of these patients suffer a relapse as early as after an average treatment period of 12-18 months. It has been shown that even the AR blocking by the currently available antiandrogens is inadequate, since the latter either have insufficient active strength and/or can even activate the androgen receptor, i.e. can act like androgens (partial agonism).

Compounds that can act as inhibitors of androgen synthesis and/or as blockers of the androgen receptor are also described in WO91/00732. In this case, these are substituted steroids, which have at least one long side chain in one of positions 6α, 7α, 14α, 15α, 16α, 17α and 17ß. Described as preferred compounds are EM 101, a testosterone that is substituted in 17ß-position with hydroxy and in 7α-position with a long-chain alkylamide, and EM 150, a testosterone that is substituted in 17ß-position with hydroxy and in 17α-position with a long-chain iodoalkine. These compounds also have the above-described drawbacks.

In summary, it has been determined that there is currently no satisfactory therapy for androgen-dependent diseases, such as, e.g., for prostate cancer, and in particular no long-term therapy is possible. The known antiandrogen compounds do not have the necessary active strength to ensure complete blocking of the androgen receptor activity or to have a partially agonistic action.

The object of this invention was therefore to provide potent antiandrogenic compounds that make possible a long-term therapy for androgen-dependent diseases. In particular, prostate cancer can be treated effectively with these compounds.

The object of this invention is achieved by new 7α-, 17α-, 17ß-substituted testosterone derivatives of general formula I



(I)

in which

R^6 represents a hydrogen atom, a hydroxy group, a C_1-C_{10} alkoxy group, a C_1-C_{10} alkanoyloxy group or a halogen atom,

R^{15} and R^{16} each are a hydrogen atom or together form a bond,

R^{17a} represents a C_1-C_4 alkyl group, a C_2-C_4 alkinyl group, or a radical of Formula $C_nF_mH_o$, whereby n = 1, 2, 3 or 4, m > 1 and m+o=2n+1,

R^{17b} is a hydroxy group, a C_1-C_{10} alkoxy group or a C_1-C_{10} alkanoyloxy group,

A is an unbranched C_6-C_{13} alkylene group,

B represents an oxygen atom, a grouping $-S(O)_p-$, whereby p = 0, 1 or 2, an iminocarbonyl group -C(O)N(Y)-, an imino group -N(Y)-, a carbonylimino group -N(Y)C(O)-, a sulfonylimino group $-N(Y)S(O)_2-$, whereby Y is a hydrogen atom or a C_1-C_8 alkyl group, a sulfonyloxy group $-OS(O)_2-$, a dimethylsilyloxy group $-O-Si(CH_3)_2-$ or a carbonylsulfanyl group -SC(O)-, or B represents a bond between A and C or together with C forms a bond between A and D,

C represents a bond between B and D, or together with B forms a bond between A and D or an unbranched C_1-C_6 alkylene group, a phenylene group, a substituted phenylene group, a five-ring or six-ring heteroarylene group, a substituted five-ring or six-ring heteroarylene group or a five-ring or six-ring heteroarylene group that is condensed with a phenyl ring,

and

D represents a hydrogen atom, a C_1-C_4 alkyl group, a vinyl group, a C_1-C_4 alkoxy group, a C_1-C_4 alkoxycarbonyl group, a bis(C_1-C_4 alkoxycarbonyl)methyl

group, an acetyl(C_1-C_4 alkoxycarbonyl)methyl group, a cyano group, a carboxy group, an azide group, a hydroxy group, a halogen atom or a radical of formula $C_nF_mH_o$, whereby n = 1, 2, 3 or 4, m > 1 and m+o=2n+1.

In a preferred embodiment of the invention, R^{17a} in general formula I means the methyl or ethyl group or the trifluoromethyl or pentafluoroethyl group. Radical R^{17b} preferably represents the hydroxy group, a C_1-C_5 alkoxy group or a C_1-C_3 alkanoyl group. Quite especially preferably, R^{17b} means the hydroxy, methoxy, ethoxy or acetyloxy group. For radical R^6, a hydrogen atom, the hydroxy group or a halogen atom is preferred. In a quite especially preferred embodiment of the invention, the radical ABCD means 9-hydroxynonyl, 7-(acetylsulfanyl)heptyl or 7-(4-cyanobutoxy)heptyl.

For the purposes of this invention, the alkylene groups that are mentioned for grouping A are the heptane-1,7-diyl, the octane-1,8-diyl, the nonane-1,9-diyl, the decane-1,10-diyl, the undecane-1,11-diyl, the dodecane-1,12-diyl and the tridecane-1,13-diyl group. The equivalent applies for the alkylene groups that are defined as grouping C.

The alkyl groups that are mentioned for substituents Y and D stand both for the unbranched groups, i.e., the methyl, ethyl and propyl group, and the corresponding higher homologues, in so far as they are claimed, and for the branched representatives of the above-mentioned carbon atom numbers, e.g., the 1-methylethyl group, the 1-methylpropyl group, the 2-methylpropyl group, the 1,1-dimethylethyl group, etc. Moreover, alkyl groups are also to

be defined as cyclic substituents, depending on the above-mentioned carbon atom number, e.g., the cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, methylcyclopentyl, cyclopentylmethyl and cyclohexyl radicals.

Alkoxy groups are radicals that are derived from the above-mentioned alkyl groups and extended by one oxygen atom, thus, e.g., the methoxy, ethoxy, propoxy, 1-methylethoxy, 1-methylpropoxy, 2-methylpropoxy and 1,1-dimethylethoxy radicals.

For the purposes of this invention, alkanoyloxy groups are defined as hydroxy groups that are esterified with branched and unbranched carboxylic acids of the above-mentioned numbers of carbon atoms, thus, e.g., the formyloxy, acetyloxy, 1-oxopropoxy, 1-oxobutoxy, and 2-methyl-1-oxopropoxy radical.

The arylene and heteroarylene groups that are indicated for grouping C are linked at a substitutable position with grouping B and substituted at another substitutable position with a radical D. Preferred heteroaromatic compounds are pyrrole, thiophene, imidazole, thiazole, oxazole, triazole, thiadiazole, indole, benzoxazole, benzothiazole, pyridine, and pyrimidine. In addition, the arylene or heteroarylene groups can be substituted with a methyl group or a halogen atom.

If a halogen atom is mentioned as a substituent in one of the radicals, a fluorine, chlorine, bromine or iodine atom is suitable for this purpose. Chlorine and fluorine are preferred.

For the purposes of the invention, the following compounds

of general formula I are quite especially preferred:

1. 7α-(9-Chlorononyl)-17α-methyl-3-oxoandrost-4-en-17ß-yl-acetate

2. 7α-(9-Chlorononyl)-17ß-hydroxy-17α-methylandrost-4-en-3-one

3. 17ß-Hydroxy-7α-(9-iodononyl)-17α-methylandrost-4-en-3-one

4. 17ß-Hydroxy-7α-(9-hydroxynonyl)-17α-methylandrost-4-en-3-one

5. 7α-(10-Chlorodecyl)-17ß-hydroxy-17α-methylandrost-4-en-3-one

6. 17ß-Hydroxy-7α-(11-hydroxyundecyl)-17α-methylandrost-4-en-3-one

7. 7α-(11-Bromoundecyl)-17ß-hydroxy-17α-methylandrost-4-en-3-one

8. 17ß-Hydroxy-17α-methyl-7α-[7-(phenylsulfanyl)heptyl]-androst-4-en-3-one

9. 17ß-Hydroxy-17α-methyl-7α-[9-[(4,4,5,5,5-pentafluoro-pentyl)sulfanyl]nonyl]androst-4-en-3-one

10. 17ß-Hydroxy-17α-methyl-7α-[9-(phenylsulfanyl)nonyl]-androst-4-en-3-one

11. 7α-[9-[(5-Chloropentyl)sulfanyl]nonyl]-17ß-hydroxy-17α-methylandrost-4-en-3-one

12. 17ß-Hydroxy-7α-[9-[(5-hydroxypentyl)sulfanyl]nonyl]-17α-methylandrost-4-en-3-one

13. 7α-(9-Azidononyl)-17ß-hydroxy-17α-methylandrost-4-en-3-one

14. 7α-[7-(Acetylsulfanyl)heptyl]-17ß-hydroxy-17α-methylandrost-4-en-3-one

15. 17ß-Hydroxy-17α-methyl-7α-[7-[(4,4,5,5,5-pentafluoropentyl)sulfanyl]heptyl]androst-4-en-3-one

16. N-[7-(17ß-Hydroxy-17α-methyl-3-oxoandrost-4-en-7α-yl)heptyl]pentanamide

17. 17ß-Hydroxy-17α-methyl-3-oxoandrost-4-en-7α-octanenitrile

18. 5-[[7-(17ß-Hydroxy-17α-methyl-3-oxoandrost-4-en-7α-yl)heptyl]oxy]pentanenitrile

19. 17ß-Hydroxy-17α-methyl-7α-[9-[(4,4,5,5,5-pentafluoropentyl)sulfinyl]nonyl]androst-4-en-3-one

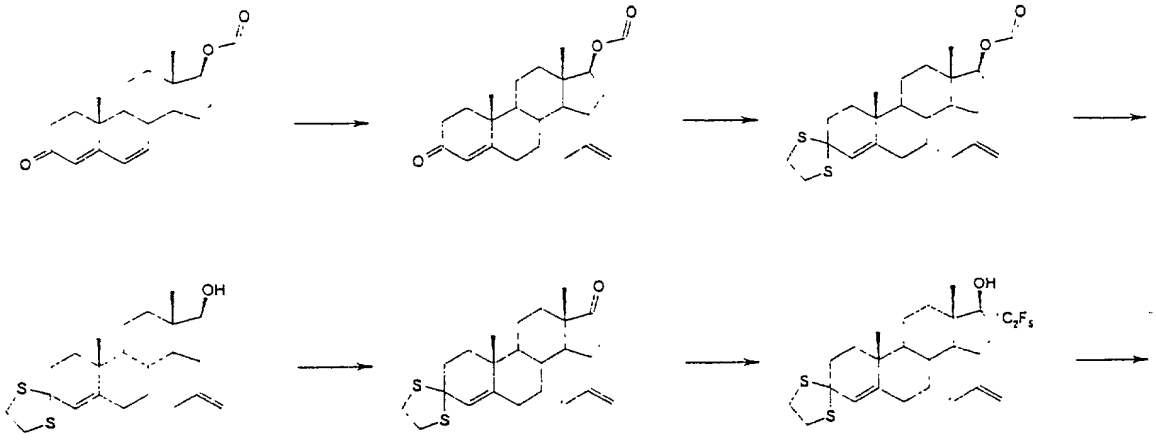
20. N-[9-(17ß-Hydroxy-17α-methyl-3-oxoandrost-4-en-7α-yl)nonyl]methanesulfonamide

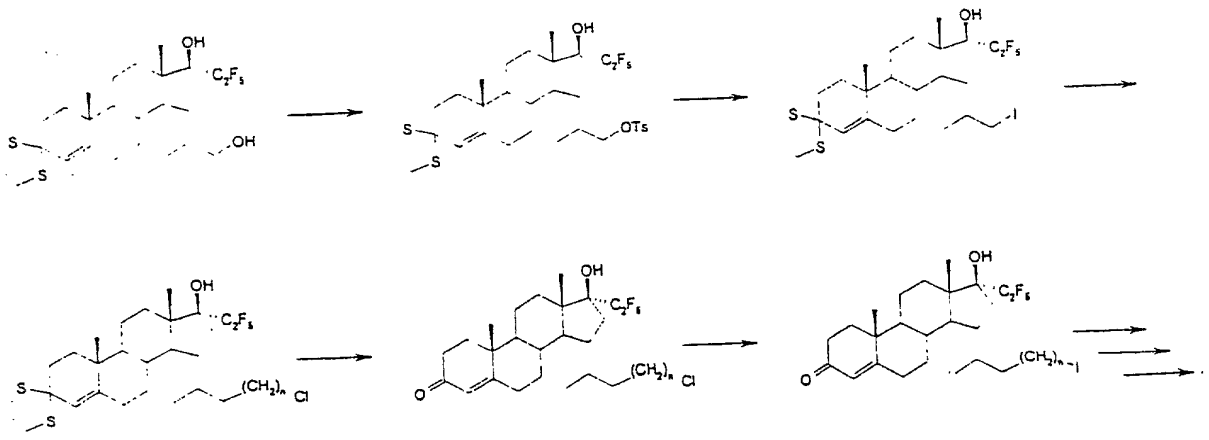
21. 7α-(9-Chlorononyl)-6ß-hydroxy-17α-methyl-3-oxoandrost-4-en-17ß-yl-acetate

The production of the compounds according to the invention is carried out analogously to the synthesis methods that are described extensively in sterol and steroid literature. The following books form the basis for steroid synthesis: L. F. Fieser & M. Fieser: Steroids: Reinhold Publishing Corporation, NY 1959; Rood's Chemistry of Carbon Compounds (editor: S. Coffrey): Elsevier Publishing Company, 1971; and especially the "Dictionary of Steroids" (editors: R. A. Hill; D. N. Kirk; H. L. J. Makin and G. M. Murphy): Chapmann & Hall. The latter contains a detailed reference list of the original publications up to 1990.

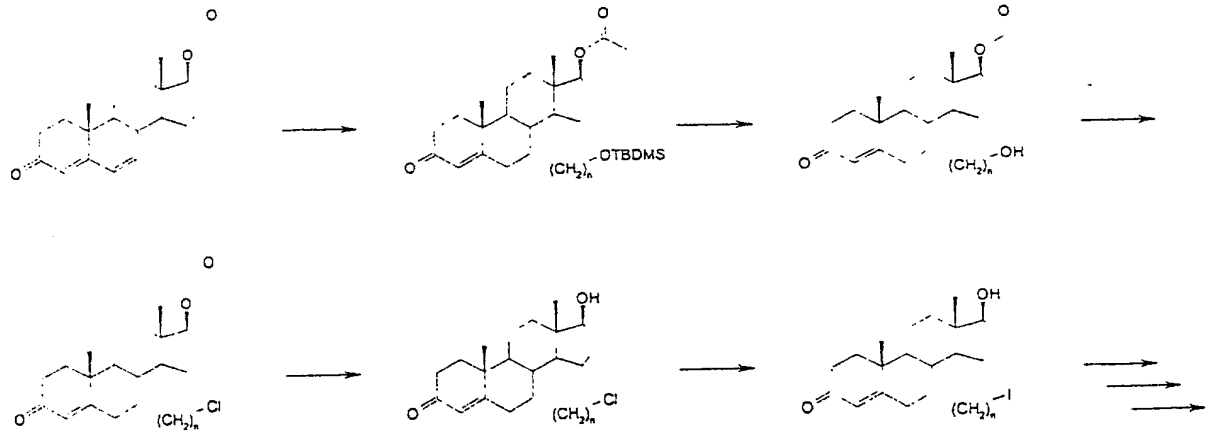
The compounds of this invention can also be produced according to the following general synthesis diagrams and analogously to the production methods that are indicated in the examples. Preferably used as a starting compound is the 3-oxoandrosta-4,6-dien-17ß-yl-acetate, whose production is described by Bowers et al. in J. Amer. Chem. Soc. 81, 5991 (1959).

For the case of the production of compounds with a perfluoroalkyl radical in 17α-position, the chain introduction in 7α-position is carried out according to Sakurai (cf. K. Nickisch, H. Laurent, Tetrahedron Lett. 29, 1533-1536 (1988)) with subsequent introduction of a carbonyl protective group in 3-position and subsequent introduction of the perfluoroalkyl radical in 17α-position according to the following diagram (cf. also Examples 1-43):





In the production of the compounds according to the invention, which have an alkyl or alkinyl group in 17α-position, the chain introduction in 7α-position can be carried out in a way that is known in the art with Grignard's reagent according to the subsequent diagram:



Additional derivatization of the alkylene iodide radical that is obtained in 7α-position is done according to commonly used organic synthesis methods and can be performed analogously to these examples.

It has now been found that the compounds of general formula I according to the invention act as pure antiandrogens and thus completely block the androgen receptor activity. The compounds completely inhibit the androgen-stimulated growth of the human prostate carcinoma cell line LNCaP. The compounds according to the invention are thus suitable for long-term antiandrogen therapy for androgen-dependent diseases, such as, for example, carcinoma of the prostate, common acne, hirsutism, early puberty, sexual deviations, androgenic alopecia, non-malignant prostatic hyperplasia or seborrhea.

The subject of the invention is therefore also the use of the compounds of general formula I according to the invention and the compounds, mentioned as preferred, for long-term antiandrogen therapy for androgen-dependent diseases, especially carcinoma of the prostate.

The compounds according to the invention are administered as pharmaceutical compositions, which contain therapeutically effective amounts of one or more compounds of general formula I and optionally galenical adjuvants and/or vehicles, which allow oral or parenteral administration of the agent. The preparations are administered in doses of 1-2000 mg, preferably 5-1000 mg per administration. The subjects of the invention are therefore also

pharmaceutical agents, which contain at least one testosterone derivative of general formula I.

The invention is to be explained in more detail in the embodiments below.

Example 1

7α-(8-Chlorooctyl)-17ß-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-3-one

1a) 3-Oxo-7α-(prop-2-enyl)androst-4-en-17ß-yl-acetate

38.6 ml of titanium tetrachloride is slowly added in drops to a solution of 23.11 g of 3-oxoandrosta-4,6-dien-17ß-yl-acetate, whose production is described in Bowers et al., **J. Amer. Chem. Soc. 81**, 5991 (1959), in 1200 ml of dichloromethane at -78°C under nitrogen atmosphere. After ten minutes of stirring, 67 ml of trimethyl(prop-2-enyl)silane is added in drops at the same temperature. The reaction mixture is stirred for two hours at -78°C and carefully mixed with water at this temperature. The organic phase is washed in succession with water, saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried on sodium sulfate, filtered and concentrated by evaporation in a vacuum. After column chromatography on silica gel with a mixture of hexane/ethyl acetate, 14.8 g of the title compound is obtained as a colorless foam.

^{1}H-NMR ($CDCl_3$): δ = 5.72 s (1H, H-4); 5.64 m (1H, allyl); 5.02 dbr (J = 10 Hz, 1H, allyl); 4.99 dbr (J = 17 Hz, 1H, allyl); 4.61 ddbr (J = 9 Hz + 8 Hz, 1H, H-17); 2.05 s (3H, acetate); 1.20 s (3H, H-19); 0.85 s (3H, H-18).

1b) 3,3-[1,2-Ethanediylbis(thio)]-7α-(prop-2-enyl)androst-4-en-17ß-yl-acetate

4.61 g of the compound that is produced under 1a) is dissolved in 50 ml of glacial acetic acid under nitrogen atmosphere and mixed with 1.04 ml of ethane-1,2-dithiol and with 1.18 g of 4-methylbenzenesulfonic acid monohydrate. The reaction mixture is stirred for four hours at room temperature, then poured onto 900 ml of 2 molar aqueous sodium hydroxide solution and extracted with dichloromethane. The organic phase is washed in succession with water and saturated aqueous sodium chloride solution, dried on sodium sulfate, filtered and concentrated by evaporation in a vacuum. Column chromatography on silica gel with a mixture of hexane/ethyl acetate yields 4.99 g of the title compound as a colorless foam.

^{1}H-NMR ($CDCl_3$): δ = 5.67 ddt (J = 17 Hz + 10 Hz + 7 Hz, 1H, allyl); 5.45 s (1H, H-4); 5.05 dbr (J = 17 Hz, 1H, allyl); 5.01 dbr (J = 10 Hz, 1H, allyl); 4.58 ddbr (J = 10 Hz + 8 Hz, 1H, H-17); 3.43-3.28 m (3H, dithiolane); 3.28-3.15 m (1H, dithiolane); 2.05 s (3H, acetate); 1.04 s (3H, H-19); 0.81 s (3H, H-18).

1c) 3,3-[1,2-Ethanediylbis(thio)]-7α-(prop-2-enyl)androst-4-en-17ß-ol

4.98 g of the compound that is described under 1b) is stirred with 1.69 g of potassium carbonate in 111 ml of methanol overnight at room temperature. The reaction mixture is largely concentrated by evaporation in a vacuum. The residue is taken up in water and extracted with ethyl acetate. The organic phase is

washed in succession with water and saturated aqueous sodium chloride solution, dried on sodium sulfate, filtered and concentrated by evaporation in a vacuum. 4.48 g of 1c) is obtained, which is used as crude product in the next step.

^{1}H-NMR ($CDCl_3$): δ = 5.67 ddt (J = 17 Hz + 10 Hz + 7 Hz, 1H, allyl); 5.44 s (1H, H-4); 5.03 dbr (J = 17 Hz, 1H, allyl); 5.01 dbr (J = 10 Hz, 1H, allyl); 3.64 m (1H, H-17); 3.45 - 3.29 m (3H, dithiolane); 3.29 - 3.15 m (1H, dithiolane); 1.05 s (3H, H-19); 0.77 s (3H, H-18).

1d) 3,3-[1,2-Ethanediylbis(thio)]-7α-(prop-2-enyl)androst-4-en-17-one

4.47 g of the compound that is produced under 1c) is dissolved in 110 ml of toluene and refluxed with 5.11 ml of cyclohexanone and with 1.01 g of aluminum triisopropylate for five hours in a water separator. For working-up, it is diluted with ethyl acetate, filtered on Celite(R), and rewashed with ethyl acetate. The filtrate is concentrated by evaporation in a vacuum. Column chromatography of the residue on silica gel with a mixture of hexane/ethyl acetate yields 4.45 g of the title compound as a colorless foam.

^{1}H-NMR ($CDCl_3$): δ = 5.69 ddt (J = 17 Hz + 10 Hz + 7 Hz, 1H, allyl); 5.48 s (1H, H-4); 5.06 dbr (J = 17 Hz, 1H, allyl); 5.04 dbr (J = 10 Hz, 1H, allyl); 3.45-3.30 m (3H, dithiolane); 3.29-3.16 m (1H, dithiolane); 2.46 dd (J = 18 Hz + 9 Hz, 1H, H-16); 1.06 s (3H, H-19); 0.89 s (3H, H-18).

1e) 3,3-[1,2-Ethanediylbis(thio)]-17α-(1,1,2,2,2-pentafluoroethyl)-7α-(prop-2-enyl)androst-4-en-17ß-ol

22 g of 1,1,1,2,2-pentafluoro-2-iodoethane is condensed in 100 ml of toluene at room temperature under nitrogen and mixed at -78°C with a solution of 4.44 g of the compound, produced under 1d), in 50 ml of toluene. After ten minutes, 51 ml of a 1.5 molar solution of methyllithium-lithium bromide complex in diethyl ether is slowly added in drops at the same temperature so that the internal temperature does not exceed -65°C. The reaction mixture is stirred in succession respectively for one hour at -78°C and at 0°C, then poured onto saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The organic phase is washed in succession with water and saturated aqueous sodium chloride solution, dried on sodium sulfate, filtered and concentrated by evaporation in a vacuum. After column chromatography on silica gel with a mixture of hexane/ethyl acetate, 5.67 g of the title compound is obtained as a colorless foam.

^{1}H-NMR ($CDCl_3$): δ = 5.66 ddt (J = 17 Hz + 10 Hz + 7 Hz, 1H, allyl); 5.45 s (1H, H-4); 5.05 dbr (J = 17 Hz, 1H, allyl); 5.02 dbr (J = 10 Hz, 1H, allyl); 3.43-3.29 m (3H, dithiolane); 3.29-3.16 m (1H, dithiolane); 2.39 m (1H, H-12); 1.04 s (3H, H-19); 0.97 s (3H, H-18).

1f) 3,3-[1,2-Ethanediylbis(thio)]-7α-(3-hydroxypropyl)-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-17ß-ol

1.1 ml of a 10 molar solution of borane-dimethyl sulfide complex in tetrahydrofuran is added in drops to a solution of 5.65 g of the compound, produced under 1e), in 110 ml of tetrahydrofuran at 0°C under nitrogen atmosphere. After 90 minutes, 22 ml of 2 molar aqueous sodium hydroxide solution and 11 ml of 30% aqueous hydrogen peroxide solution are slowly added in drops at 0°C. The reaction mixture is stirred for one hour at 0°C, diluted with water and extracted with ethyl acetate. The organic phase is washed in succession with water and saturated aqueous sodium chloride solution, dried on sodium sulfate, filtered and concentrated by evaporation in a vacuum. Column chromatography on silica gel with a mixture of hexane/ethyl acetate yields 2.34 g of the title compound as a colorless foam.

^{1}H-NMR ($CDCl_3$): δ = 5.48 s (1H, H-4); 3.64 m (2H, CH_2OH); 3.43-3.28 m (3H, dithiolane); 3.28-3.16 m (1H, dithiolane); 2.39 m (1H, H-12); 1.04 s (3H, H-19); 0.96 s (3H, H-18).

1g) 3-[3,3-[1,2-Ethanediylbis(thio)]-17ß-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-7α-yl]propyl-(4-methylbenzenesulfonate)

2.3 g of the compound that is produced under 1f) is stirred with 3.26 g of 4-methylbenzenesulfonyl chloride and 6 ml of triethylazan in 85 ml of dichloromethane for four hours at room temperature under nitrogen atmosphere. The reaction mixture is poured into saturated aqueous sodium bicarbonate solution and

extracted with ethyl acetate. The organic phase is washed in succession with water and saturated aqueous sodium chloride solution, dried on sodium sulfate, filtered and concentrated by evaporation in a vacuum. Column chromatography on silica gel with a mixture of hexane/ethyl acetate yields 1.8 g of the title compound as a colorless foam.

^{1}H-NMR ($CDCl_3$): δ = 7,81 d (J = 9 Hz, 2H, aryl); 7.37 d (J = 9 Hz, 2H, aryl); 5.40 s (1H, H-4); 4.06 m (2H, CH_2OTs); 3.43-3.29 m (3H, dithiolane); 3.29-3.16 m (1H, dithiolane); 2.46 s (3H, tolyl); 2.36 m (1H, H-12); 1.02 s (3H, H-19); 0.94 s (3H, H-18).

1h) 3,3-[1,2-Ethanediylbis(thio)]-7α-(3-iodopropyl)-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-17ß-ol

1.75 g of the compound that is produced under 1g) is refluxed overnight with 490 mg of sodium iodide in 25 ml of acetone. The reaction mixture is filtered, and the filtrate is concentrated by evaporation in a vacuum. Column chromatography on silica gel with a mixture of hexane/ethyl acetate yields 1.36 g of the title compound as a colorless foam.

^{1}H-NMR ($CDCl_3$): δ = 5.48 s (1H, H-4); 3.44-3.29 m (3H, dithiolane); 3.29-3.15 m (1H, dithiolane); 3.18 t (J = 7 Hz, 2H, CH_2I); 2.40 m (1H, H-12); 1.04 s (3H, H-19); 0.96 s (3H, H-18).

1i) 7α-(8-Chlorooctyl)-3,3-[1,2-ethanediylbis(thio)]-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-17ß-ol

A solution of the Grignard compound 5-chloropentylmagnesium bromide is produced from 214 mg of magnesium chips in 2.2 ml of tetrahydrofuran by adding in drops a solution of 1.16 ml of 1-bromo-5-chloropentane in 6.6 ml of tetrahydrofuran at an internal temperature below 35°C and with thirty more minutes of stirring. In another flask, a brown solution of dilithium tetrachlorocuprate is produced from 7.5 mg of lithium chloride and 11.8 mg of anhydrous copper(II) chloride in 0.88 ml of tetrahydrofuran by fifteen minutes of stirring at room temperature. 575 mg of the compound that is produced under 1h) and dissolved in 2 ml of tetrahydrofuran is added in drops to the above. At -10°C, the Grignard solution is added in drops to the steroid solution within one hour. During one more hour of stirring time, the reaction mixture reaches 0°C. It is then poured into saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic phase is washed in succession with water and saturated aqueous sodium chloride solution, dried on sodium sulfate, filtered and concentrated by evaporation in a vacuum. After column chromatography on silica gel with a mixture of hexane/ethyl acetate, 342 mg of the title compound is obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 5.46 s (1H, H-4); 3.54 t (J = 7 Hz, 2H, CH_2Cl); 3.43-3.29 m (3H, dithiolane); 3.29-3.14 m (1H, dithiolane); 2.39 m (1H, H-12); 1.05 s (3H, H-19); 0.97 s (3H, H-18).

1j) 7α-(8-Chlorooctyl)-17ß-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-3-one

330 mg of the compound that is produced under 1i) is dissolved in 16 ml of glacial acetic acid, mixed with 2.43 g of glyoxylic acid and stirred for 15 minutes at room temperature. Then, 2 ml of 4 molar aqueous hydrochloric acid is added. After one hour of stirring at room temperature, the reaction mixture is added in drops to 500 ml of 2 molar aqueous sodium hydroxide solution and extracted with ethyl acetate. The organic phase is washed in succession with water and saturated aqueous sodium chloride solution, dried on sodium sulfate, filtered and concentrated by evaporation in a vacuum. Column chromatography on silica gel with a mixture of hexane/ethyl acetate yields 172 mg of the title compound as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 5.73 s (1H, H-4); 3.54 t (J = 7 Hz, 2H, CH_2Cl); 1.21 s (3H, H-19); 1.00 s (3H, H-18).

Example 2

17ß-Hydroxy-7α-(8-iodooctyl)-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-3-one

161 mg of the compound that is produced under 1j) is heated overnight to 80°C with 87 mg of sodium iodide in 3 ml of 2-butanone. The reaction mixture is diluted with water and extracted with ethyl acetate. The organic phase is washed in succession with water and saturated aqueous sodium chloride solution, dried on sodium sulfate, filtered and concentrated by evaporation in a vacuum. Column chromatography on silica gel

with a mixture of hexane/ethyl acetate yields 182 mg of the title compound as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 5.72 s (1H, H-4); 3.19 t (J = 7 Hz, 2H, CH_2I); 1.21 s (3H, H-19); 1.00 s (3H, H-18).

Example 3

17ß-Hydroxy-3-oxo-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-7α-nonane nitrile

30 mg of the compound that is produced under 2) is stirred with 9 mg of potassium cyanide in 1 ml of N,N-dimethylformamide for 16 hours at room temperature. The reaction mixture is diluted with water and extracted with ethyl acetate. The organic phase is washed with saturated aqueous sodium chloride solution, dried on sodium sulfate, filtered and concentrated by evaporation in a vacuum. Column chromatography on silica gel with a mixture of hexane/ethyl acetate yields 20 mg of the title compound as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 5.72 s (1H, H-4); 2.34 t (J = 7 Hz, 2H, CH_2CN); 1.21 s (3H, H-19); 1.00 s (3H, H-18).

Example 4

17ß-Hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-7α-[8-(phenylsulfanyl)octyl]androst-4-en-3-one

80 mg of the compound that is produced under 2) is stirred with 22 mg of sodium phenyl thiolate in 1.5 ml of ethanol for 16 hours at 60°C. The reaction mixture is concentrated by evaporation in a vacuum and taken up in ethyl acetate. The

organic phase is washed in succession with water and saturated aqueous sodium chloride solution, dried on sodium sulfate, filtered and concentrated by evaporation in a vacuum. Column chromatography on silica gel with a mixture of hexane/ethyl acetate yields 66 mg of the title compound as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 7.36-7.24 m (4H, aryl); 7.17 ddbr (J = 8 Hz + 8 Hz, 1H, aryl); 5.73 s (1H, H-4); 2.92 t (J = 7 Hz, 2H, CH_2S); 1.21 s (3H, H-19); 1.00 s (3H, H-18).

Example 5

17ß-Hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-7α-[8-(phenylsulfinyl)octyl]androst-4-en-3-one

36 mg of the compound that is produced under 4) is dissolved in 0.34 ml of tetrahydrofuran, mixed with a solution of 55 mg of sodium periodate in 86 µl of water and 0.34 ml of methanol and stirred for 18 hours at room temperature. The reaction mixture is filtered, rewashed with ethyl acetate and concentrated by evaporation in a vacuum. The residue is taken up in ethyl acetate and water. The organic phase is washed with saturated aqueous sodium chloride solution, dried on sodium sulfate, filtered and concentrated by evaporation in a vacuum. After column chromatography on silica gel with a mixture of hexane/ethyl acetate, 20 mg of the title compound is obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 7.61 dbr (J = 8 Hz, 2H, aryl); 7.57-7.45 m (3H, aryl); 5.72 s (1H, H-4); 2.79 t (J = 7 Hz, 2H, CH_2SO); 1.21 s (3H, H-19); 1.00 s (3H, H-18).

Example 6

7α-[8-[(2-Chlorophenyl)sulfanyl]octyl]-17ß-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-3-one

5.9 µl of 2-chlorobenzenethiol is added to a suspension of 2.1 mg of 60% sodium hydride as a dispersion in mineral oil in 1 ml of N,N-dimethylformamide. After one hour at room temperature, 30 mg of the compound that is produced under 2) and dissolved in 1 ml of N,N-dimethylformamide is added. The reaction mixture is stirred for 14 hours at room temperature, diluted with water and extracted with ethyl acetate. The organic phase is washed with saturated aqueous sodium chloride solution, dried on sodium sulfate, filtered and concentrated by evaporation in a vacuum. Column chromatography on silica gel with a mixture of hexane/ethyl acetate yields 17 mg of the title compound as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 7.36 dbr (J = 8 Hz, 1H, aryl); 7.26 dbr (J = 8 Hz, 1H, aryl); 7.22 ddbr (J = 8 Hz + 8 Hz, 1H, aryl); 7.09 ddbr (J = 8 Hz + 8 Hz, 1H, aryl); 5.73 s (1H, H-4); 2.93 t (J = 7 Hz, 2H, CH_2S); 1.21 s (3H, H-19); 1.00 s (3H, H-18).

The following compounds were obtained analogously:

Ex.	Product Reagent (Precursor/Process)	Form	Yield [%]	^{1}H-NMR δ
7	17ß-Hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-7α-[8-[(pyridin-2-yl)sulfanyl]octyl]androst-4-en-3-one Pyridine-2-thiol (2\6)	Foam	41	8.42 dbr (J = 5Hz, 1H, pyridinyl); 7.47 ddd (J = 8Hz + 8Hz + 2Hz, 1H, pyridinyl); 7.17 dbr (J = 8Hz, 1H, pyridinyl); 6.96 ddbr (J = 8Hz + 5 Hz, 1H, pyridinyl); 5.72 s (1H, H-4); 3.15 t (J = 7Hz, 2H, CH_2S); 1.20 s (3H, H-19); 0.99 s (3H, H-18)
8	17ß-Hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-7α-[8-[(pyrimidin-2-yl)sulfanyl]octyl]androst-4-en-3-one Pyrimidine-2-thiol (2\6)	Oil	31	8.50 d (J = 5Hz, 2H, pyrimidinyl); 6.95 t (J = 5Hz, 1H, pyrimidinyl); 5.72 s (1H, H-4); 3.14 t (J = 7Hz, 2H, CH_2S); 1.21 s (3H, H-19); 1.00 s (3H, H-18)

9	7α-[8-[(Benzothiazol-2-yl)sulfanyl]-octyl]-17ß-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-3-one Benzothiazole-2-thiol (2\6)	Oil	53	7.87 dbr (J= 8Hz, 1H, aryl); 7.76 dbr (J = 8Hz, 1H, aryl); 7.41 ddbr (J = 8Hz + 8Hz, 1H, aryl); 7.29 ddbr (J = 8Hz + 8Hz, 1H, aryl); 5.73 s (1H, H-4); 3.34 t (J = 7Hz, 2H, CH_2S); 1.21 s (3H, H-19); 1.00 s (3H, H-18)
10	7α-[8-[(6-Ethoxybenzothiazol-2-yl)sulfanyl]octyl]-17ß-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-3-one 6-Ethoxybenzothiazole-2-thiol (2\6)	Foam	37	7.74 d (J = 9Hz, 1H, aryl); 7.22 d (J = 2Hz, 1H, aryl); 7.01 dd (J = 9Hz + 2Hz, 1H, aryl); 5.73 s (1H, H-4); 4.08 q (J = 7Hz, 2H, OEt); 3.31 t (J = 7Hz, 2H, CH_2S); 1.44 t (J = 7Hz, 3H, OEt); 1.21 s (3H, H-19); 1.00 s (3H, H-18)

11	17ß-Hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-7α-[8-[(thiazol-2-yl)sulfanyl]octyl]androst-4-en-3-one Thiazole-2-thiol (2\6)	Oil	51	7.66 d (J = 3Hz, 1H, thiazolyl); 7.20 d (J = 3Hz, 1H, thiazolyl); 5.73 s (1H, H-4); 3.20 t (J = 7 Hz, 2H, CH_2S); 1.21 s (3H, H-19); 1.00 s (3H, H-18)
12	17ß-Hydroxy-7α-[8-[(1-methyl-1H-imidazol-2-yl)sulfanyl]octyl]-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-3-one 1-Methyl-1H-imidazole-2-thiol (2\6)	Oil	57	7.05 d (J = 1Hz, 1H, imidazolyl); 6.92 d (J = 1Hz, 1H, imidazolyl); 5.72 s (1H, H-4); 3.62 s (3H, Me); 3.03 t (J = 7 Hz, 2H, CH_2S); 1.21 s (3H, H-19); 1.00 s (3H, H-18)
13	17ß-Hydroxy-7α-[8-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]octyl]-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-3-one 5-Methyl-1,3,4-thiadiazole-2-thiol (2\6)	Oil	60	5.72 s (1H, H-4); 2.72 s (3H, thiadiazolyl); 3.28 t (J = 7Hz, 2H, CH_2S); 1.21 s (3H, H-19); 1.00 s (3H, H-18)

14	17ß-Hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-7α-[8-[(thien-2-yl)sulfanyl]octyl]androst-4-en-3-one Thiophene-2-thiol (2\6)	Oil	20	7.32 dd (J = 5Hz + 1Hz, 1H, thienyl); 7.10 dd (J = 4Hz + 1Hz, 1H, thienyl); 6.97 dd (J = 5Hz + 4Hz, 1H, thienyl); 5.72 s (1H, H-4); 2.79 t (J = 7Hz, 2H, CH_2S); 1.21 s (3H, H-19); 1.00 s (3H, H-18)
15	2,2,3,3,4,4,4-Heptafluoro-N-[8-[17ß-hydroxy-3-oxo-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-7α-yl]octyl]butanamide 2,2,3,3,4,4,4-Heptafluorobutanamide (2\6)	Oil	62	6.71 sbr (1H, NH); 5.72 s (1H, H-4); 3.38 m (2H, CH_2N); 1.21 s (3H, H-19); 1.00 s (3H, H-18)

16	17ß-Hydroxy-7α-[8-[(4-methyl-phenyl)sulfonyl]-octyl]-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-3-one Sodium-4-methyl-benzenesulfinate (2\4)	Oil	64	7.79 dbr (J = 8Hz, 2H, aryl); 7.36 dbr (J = 8Hz, 2H, aryl); 5.71 s (1H, H-4); 3.06 m (2H, CH_2SO_2); 2.45 s (3H, tolyl); 1.21 s (3H, H-19); 1.00 s (3H, H-18)
17	17ß-Hydroxy-7α-[8-[(3-methyl-phenyl)sulfonyl]-octyl]-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-3-one Sodium-3-methylbenzene-sulfinate, for production see B. Lindberg, **Acta Chem. Scand.17**, 377-382 (1963) (2\4)	Oil	22	7.62 sbr (1H, aryl); 7.61 m (1H, aryl); 7.46 m (2H, aryl); 5.72 s (1H, H-4); 3.06 m (2H, CH_2SO_2); 2.46 s (3H, tolyl); 1.21 s (3H, H-19); 1.00 s (3H, H-18)

18a	7α-(10-Bromodecyl)-3,3-[1,2-ethanediylbis(thio)]-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-17ß-ol 7-Bromoheptylmagnesium bromide (1h\1i)	Oil	87	5.46 s (1H, H-4); 3.45-3.29 m (3H, dithiolane); 3.29-3.15 m (1H, dithiolane); 3.46 t (J = 7Hz, 2H, CH_2Br); 2.39 m (1H, H-12); 1.04 s (3H, H-19); 0.96 s (3H, H-18)
18b	7α-(10-Bromodecyl)-17ß-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-3-one Glyoxylic acid/ glacial acetic acid (18a\1j)	Oil	22	5.73 s (1H, H-4); 3.41 t (J = 7 Hz, 2H, CH_2Br); 1.21 s (3H, H-19); 1.00 s (3H, H-18)
19	17ß-Hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-7α-[10-(phenylsulfanyl)decyl]androst-4-en-3-one Sodium phenylthiolate (18b\4)	Oil	76	7.31 dbr (J = 8Hz, 2H, aryl); 7.27 ddbr (J = 8Hz + 8Hz, 2H, aryl); 7.16 ddbr (J = 8Hz + 8Hz, 1H, aryl); 5.73 s (1H, H-4); 2.91 t (J = 7Hz, 2H, CH_2S); 1.21 s (3H, H-19); 0.99 s (3H, H-18)

20	17ß-Hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-7α-[10-(phenyl-sulfinyl)decyl]androst-4-en-3-one Sodium periodate (19\5)	Oil	22	7.61 dbr (J = 8Hz, 2H, aryl); 7.57-7.48 m (3H, aryl); 5.73 s (1H, H-4); 2.78 t (J = 7Hz, 2H, CH_2SO); 1.20 s (3H, H-19); 1.00 s (3H, H-18)
21a	3,3-[1,2-Ethanediylbis(thio)]-7α-(8-iodooctyl)-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-17ß-ol Sodium iodide (1i\2)	Oil	83	5.46 s (1H, H-4); 3.43-3.29 m (3H, dithiolane); 3.29-3.14 m (1H, dithiolane); 3.18 t (J = 7Hz, 2H, CH_2I); 2.39 m (1H, H-12); 1.05 s (3H, H-19); 0.97 s (3H, H-18)
21b	7α-(13-Clortridecyl)-3,3-[1,2-ethanediylbis(thio)]-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-17ß-ol 5-Chloropentyl-magnesium bromide (21a\1i)	Oil	43	5.46 s (1H, H-4); 3.54 t (J = 7Hz, 2H, CH_2Cl); 3.43-3.29 m (3H, dithiolane); 3.29-3.14 m (1H, dithiolane); 2.39 m (1H, H-12); 1.05 s (3H, H-19); 0.97 s (3H, H-18)

21c	7α-(13-Chlorotridecyl)-17ß-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-3-one Glyoxylic acid/ glacial acetic acid (21b\1j)	Oil	72	5.73 s (1H, H-4); 3.54 t (J = 7Hz, 2H, CH_2Cl); 1.21 s (3H, H-19); 1.00 s (3H, H-18)
22	17ß-Hydroxy-7α-(13-iodotridecyl)-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-3-one Sodium iodide (21c\2)	Oil	86	5.72 s (1H, H-4); 3.19 t (J = 7Hz, 2H, CH_2I); 1.21 s (3H, H-19); 1.00 s (3H, H-18)
23	17ß-Hydroxy-3-oxo-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-ene-7α-tetradecane nitrile Potassium cyanide (22\3)	Oil	82	5.73 s (1H, H-4); 2.34 t (J = 7Hz, 2H, CH_2CN); 1.21 s (3H, H-19); 1.00 s (3H, H-18)
24	17ß-Hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-7α-[13-(phenylsulfanyl)tridecyl]androst-4-en-3-one Sodium phenyl thiolate (22\4)	Oil	87	7.36-7.22 m (4H, aryl); 7.15 ddbr (J = 8 Hz + 8 Hz, 1H, aryl); 5.73 s (1H, H-4); 2.91 t (J = 7Hz, 2H, CH_2S) 1.21 s (3H, H-19); 1.00 s (3H, H-18)

25	17ß-Hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-7α-[13-[(3-methyl-phenyl)sulfanyl]-tridecyl]androst-4-en-3-one 3-Methylbenzenethiol (22\6)	Oil	47	7.18 ddbr (J = 8Hz + 8Hz, 1H, aryl); 7.14 sbr (1H, aryl); 7.12 dbr (J = 8Hz, 1H, aryl); 6.98 dbr (J = 8Hz, 1H, aryl); 5.74 s (1H, H-4); 2.91 t (J = 7Hz, 2H, CH_2S); 2.32 s (1H, tolyl); 1.21 s (3H, H-19); 1.00 s (3H, H-18)
26	17ß-Hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-7α-[13-[(pyridin-2-yl)sulfanyl]tridecyl]androst-4-en-3-one Pyridine-2-thiol (22\6)	Oil	44	8.42 dbr (J = 5Hz, 1H, pyridinyl); 7.47 ddd (J = 8Hz + 8Hz + 2Hz, 1H, pyridinyl); 7.17 dbr (J = 8Hz, 1H, pyridinyl); 6.97 ddbr (J = 8Hz + 5Hz, 1H, pyridinyl); 5.73 s (1H, H-4); 3.15 t (J = 7Hz, 2H, CH_2S); 1.21 s (3H, H-19); 0.99 s (3H, H-18)

27	17ß-Hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-7α-[13-[(pyrimidin-2-yl)sulfanyl]tridecyl]androst-4-en-3-one Pyrimidine-2-thiol (22\6)	Oil	31	8.50 d (J = 5Hz, 2H, pyrimidinyl); 6.94 t (J = 5Hz, 1H, pyrimidinyl); 5.72 s (1H, H-4); 3.13 t (J = 7Hz, 2H, CH_2S); 1.21 s (3H, H-19); 1.00 s (3H, H-18)
28	17ß-Hydroxy-7α-[13-[(1-methyl-1H-imidazol-2-yl)sulfanyl]tridecyl]-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-3-one 1-Methyl-1H-imidazole-2-thiol (22\6)	Oil	27	7.06 sbr (1H, imidazolidinyl); 6.92 sbr (1H, imidazolidinyl); 5.73 s (1H, H-4); 3.62 s (3H, NCH_3); 3.04 t (J = 7 Hz, 2H, CH_2S); 1.21 s (3H, H-19); 1.00 s (3H, H-18)

29	7α-[13-[(Benzothiazol-2-yl)sulfanyl]tridecyl]-17ß-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-3-one Benzothiazole-2-thiol (22\6)	Oil	35	7.87 dbr (J = 8Hz, 1H, aryl); 7.76 dbr (J = 8Hz, 1H, aryl); 7.41 ddbr (J = 8Hz + 8Hz, 1H, aryl); 7.31 ddbr (J = 8Hz + 8Hz, 1H, aryl); 5.75 s (1H, H-4); 3.34 t (J = 7Hz, 2H, CH_2S); 1.21 s (3H, H-19); 1.00 s (3H, H-18)
30	7α-[13-[(6-Ethoxybenzothiazol-2-yl)sulfanyl]tridecyl]-17ß-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-3-one 6-Ethoxybenzothiazole-2-thiol (22\6)	amorphous	70	7.74 d (J = 9Hz, 1H, aryl); 7.22 d (J = 2Hz, 1H, aryl); 7.01 dd (J = 9Hz + 2Hz, 1H, aryl); 5.73 s (1H, H-4); 4.07 q (J = 7Hz, 2H, OEt); 3.30 t (J = 7Hz, 2H, CH_2S); 1.44 t (J = 7Hz, 3H, OEt); 1.21 s (3H, H-19); 1.00 s (3H, H-18)

31	17ß-Hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-7α-[13-[(thiazol-2-yl)sulfanyl]tridecyl]androst-4-en-3-one Thiazole-2-thiol (22\6)	Oil	85	7.66 d (J = 3Hz, 1H, thiazolyl); 7.20 d (J = 3Hz, 1H, thiazolyl); 5.73 s (1H, H-4); 3.20 t (J = 7Hz, 2H, CH_2S); 1.21 s (3H, H-19); 1.00 s (3H, H-18)
32	17ß-Hydroxy-7α-[13-[(4-methyl-phenyl)sulfonyl]tri-decyl]-17α-(1,1,2,2,2-pentafluoroethyl)an-drost-4-en-3-one Sodium-4-methylbenzene-sulfinate (22\4)	Foam	51	7.78 dbr (J = 8Hz, 2H, aryl); 7.37 dbr (J = 8Hz, 2H, aryl); 5.73 s (1H, H-4); 3.06 m (2H, CH_2SO_2); 2.46 s (3H, tolyl); 1.21 s (3H, H-19); 1.00 s (3H, H-18)

33a	3,3-[1,2-Ethane-diylbis(thio)]-7α-(hex-5-enyl)-17α-(1,1,2,2,2-pentafluoroethyl)an-drost-4-en-17ß-ol Prop-2-enylmagnesium bromide (1h\1i)	Foam	81	5.82 ddt (J = 17Hz + 10Hz + 7Hz, 1H, vinyl); 5.46 s (1H, H-4); 5.02 dbr (J = 17Hz, 1H, vinyl); 4.94 dbr (J = 10Hz, 1H, vinyl); 3.45-3.29 m (3H, dithiolane); 3.29-3.16 m (1H, dithiolane); 2.39 m (1H, H-12); 1.05 s (3H, H-19); 0.96 s (3H, H-18)
33b	3,3-[1,2-Ethane-diylbis(thio)]-7α-(3-hydroxyhexyl)-17α-(1,1,2,2,2-pentafluoroethyl)an-drost-4-en-17ß-ol Borane-dimethyl sulfide complex (33a\1f)	Foam	69	5.45 s (1H, H-4); 3.64 tbr (J = 6Hz, 2H, CH_2OH); 3.44-3.29 m (3H, dithiolane); 3.29-3.16 m (1H, dithiolane); 2.39 m (1H, H-12); 1.04 s (3H, H-19); 0.96 s (3H, H-18)

33c	6-[17ß-Hydroxy-3-oxo-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-7α-yl]hexyl-acetate Glyoxylic acid/ Glacial acetic acid (33b\1j)	amorphous	66	5.73 s (1H, H-4); 4.05 t (J = 7Hz, 2H, CH_2O); 2.05 s (3H, acetate); 1.21 s (3H, H-19); 1.00 s (3H, H-18)
34	17ß-Hydroxy-7α-(6-hydroyxhexyl)-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-3-one Potassium carbonate/methanol (33c\1c)	Foam	62	5.74 s (1H, H-4); 3.64 t (J = 7Hz, 2H, CH_2O); 1.21 s (3H, H-19); 1.00 s (3H, H-18)
35	6-[17ß-Hydroxy-3-oxo-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-7α-yl]hexyl-(4-methylbenzene-sulfonate) 4-Methylbenzene-sulfonyl chloride (34\1g)	Foam	87	7.79 d (J = 8Hz, 2H, aryl); 7.35 d (J = 8Hz, 2H, aryl); 5.71 s (1H, H-4); 4.01 t (J = 7Hz, 2H, CH_2OTs); 2.46 s (3H, tolyl); 1.21 s (3H, H-19); 1.00 s (3H, H-18)

36	17ß-Hydroxy-7α-(6-iodohexyl)-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-3-one Sodium iodide (35\2)	Foam	92	5.73 s (1H, H-4); 3.19 t (J = 7Hz, 2H, CH_2I); 1.21 s (3H, H-19); 1.00 s (3H, H-18)
37	17ß-Hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-7α-[6-(phenylsulfanyl)hexyl]androst-4-en-3-one Sodium phenyl thiolate (36\4)	Oil	14	7.31 dbr (J = 8Hz, 2H, aryl); 7.27 ddbr (J = 8Hz + 8Hz, 2H, aryl); 7.16 ddbr (J = 8Hz + 8Hz, 1H, aryl); 5.72 s (1H, H-4); 2.91 t (J = 7Hz, 2H, CH_2S); 1.20 s (3H, H-19); 1.00 s (3H, H-18)
38	17ß-Hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-7α-[6-(phenylsulfonyl)hexyl]androst-4-en-3-one Sodium benzene sulfinate (36\4)	Oil	78	7.91 dbr (J = 8Hz, 2H, aryl); 7.67 ddbr (J = 8Hz + 8Hz, 1H, aryl); 7.58 ddbr (J = 8Hz + 8Hz, 2H, aryl); 5.69 s (1H, H-4); 3.08 m (2H, CH_2SO_2); 1.20 s (3H, H-19); 1.00 s (3H, H-18)

39	17ß-Hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-7α-[6-[(pyridin-2-yl)sulfanyl]hexyl]androst-4-en-3-one Pyridine-2-thiol (36\6)	Oil	58	8.42 dbr (J = 5Hz, 1H, pyridinyl); 7.47 ddd (J = 8Hz + 8Hz + 2Hz, 1H, pyridinyl); 7.18 dbr (J = 8Hz, 1H, pyridinyl); 6.97 ddbr (J = 8Hz + 5Hz, 1H, pyridinyl); 5.72 s (1H, H-4); 3.05 t (J = 7Hz, 2H, CH_2S); 1.20 s (3H, H-19); 1.00 s (3H, H-18)
40	17ß-Hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-7α-[6-[(pyrimidin-2-yl)sulfanyl]hexyl]androst-4-en-3-one Pyrimidine-2-thiol (36\6)	Oil	82	8.50 d (J = 5Hz, 2H, pyrimidinyl); 6.94 t (J = 5Hz, 1H, pyrimidinyl); 5.72 s (1H, H-4); 3.12 t (J = 7Hz, 2H, CH_2S); 1.20 s (3H, H-19); 1.00 s (3H, H-18)

41	7α-[6-[(4,6-Dimethylpyrimidin-2-yl)sulfanyl]hexyl]-17ß-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-3-one 4,6-Dimethylpyrimidine-2-thiol (36\6)	Oil	56	6.67 s (1H, pyrimidinyl); 5.73 s (1H, H-4); 3.25 t (J = 7Hz, 2H, CH_2S); 2.40 s (6H, Me); 1.20 s (3H, H-19); 1.00 s (3H, H-18)
42	17ß-Hydroxy-7α-[6-[(1-methyl-1H-imidazol-2-yl)sulfanyl]hexyl]-17α-(1,1,2,2,2-pentafluoroethyl)androst-4-en-3-one 1-Methyl-1H-imidazole-2-thiol (36\6)	Oil	20	7.05 d (J = 1Hz, 1H, imidazolyl); 6.92 d (J = 1Hz, 1H, imidazolyl); 5.71 s (1H, H-4); 3.62 s (3H, Me); 3.04 t (J = 7Hz, 2H, CH_2S); 1.20 s (3H, H-19); 1.00 s (3H, H-18)
43	17ß-Hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-7α-[6-[(thiazol-2-yl)sulfanyl]hexyl]androst-4-en-3-one Thiazole-2-thiol (36\6)	Oil	68	7.65 d (J = 4 Hz, 1H, thiazolyl); 7.21 d (J = 4Hz, 1H, thiazolyl); 5.72 s (1H, H-4); 3.20 t (J = 7Hz, 2H, CH_2S); 1.20 s (3H, H-19); 1.00 s (3H, H-18)

Example 44

7α-[9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]nonyl]-17α-methyl-3-oxoandrost-4-en-17ß-yl-acetate

2.82 g of magnesium chips (116 mmol) is suspended in 56 ml of dry tetrahydrofuran, and the formation of the Grignard compound is begun with a little [(9-bromononyl)oxy](1,1-dimethylethyl)dimethylsilane, some dibromomethane and some granules of iodine. After the start-up, the solution of a total of 39.0 g of [(9-bromononyl)oxy](1,1-dimethylethyl)dimethylsilane (116 mmol) in 36 ml of dry tetrahydrofuran is added drop by drop so that the internal temperature does not exceed 35°C. Then, the solution is heated for 15 minutes to 80°C and then mixed at -60°C with a solution that was prepared from 11.0 g of copper(I) iodide (58 mmol) in 54 ml of dry tetrahydrofuran by adding 20.1 g of lithium bromide (132 mmol) while being cooled with ice and diluted with 21 ml of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone. With the addition, the internal temperature is not to exceed -50°C. After 15 minutes of stirring at -20°C, it is cooled to -70°C, and the solution of 17α-methyl-3-oxoandrosta-4,6-dien-17ß-yl acetate (40 mmol), whose production is described in V. Schwarz, **Collect. Czech. Chem. Commun. 26**, 1958-1966 (1961), and 13 ml of chlorotrimethylsilane in 60 ml of dry tetrahydrofuran and 16 ml of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone are quickly added so that the internal temperature does not exceed -65°C. The mixture is stirred for one hour, whereby the temperature reaches -50°C, and finally it is mixed with 16 ml of glacial acetic acid and left for another

hour at room temperature. Then, the batch is diluted with ethyl acetate, shaken out with semisaturated aqueous ammonium chloride solution, with 2 molar aqueous ammonia solution and twice with saturated aqueous common salt solution, the organic phase is dried with sodium sulfate and concentrated by evaporation. The residue is chromatographed on silica gel with dichloromethane/hexane, and the yield is 13.9 g (57% of theory) of the title compound. Then, 4 g of 7ß-[9-[[(1,1-dimethylethyl)dimethylsilyl]oxy]nonyl]-17α-methyl-3-oxoandrost-4-en-17ß-yl acetate (15% of theory) is isolated. Both compounds are oily and were characterized by MS: Cld. 600, Fnd. 600.

The following compounds were obtained analogously:

Ex.	Product Reagent (Precursor/Process)	Form	Yield [%]	MS	
				Cld.	Fnd.
45	7α-[7-[[(1,1-Dimethylethyl)dimethyl-silyl]oxy]heptyl]-17α-methyl-3-oxoandrost-4-en-17ß-yl-acetate [(7-Bromoheptyl)oxy](1,1-dimethylethyl)dimethylsilane (17α-Methyl-3-oxoandrosta-4,6-dien-17ß-yl-acetate\44)	Oil	51	572	572
46	7α-[10-[[(1,1-Dimethylethyl)dimethyl-silyl]oxy]decyl]-17α-methyl-3-oxoandrost-4-en-17ß-yl-acetate [(10-Bromodecyl)oxy](1,1-dimethylethyl)dimethylsilane (17α-Methyl-3-oxoandrosta-4,6-dien-17ß-yl-acetate\44)	Oil	56	615	615
47	7α-[11-[[(1,1-Dimethylethyl)dimethyl-silyl]oxy]undecyl]-17α-methyl-3-oxoandrost-4-en-17ß-yl acetate [(11-Bromoundecyl)oxy](1,1-dimethylethyl)dimethylsilane (17α-Methyl-3-oxoandrosta-4,6-dien-17ß-yl-acetate\44)	Oil	60	629	629

48	7α-[7-(4-Chlorobutoxy)heptyl]-17α-methyl-3-oxoandrost-4-en-17ß-yl-acetate 1-Bromo-7-(4-chlorobutoxy)heptane (17α-Methyl-3-oxoandrosta-4,6-dien-17ß-yl-acetate\44)	Oil	51	548 550	548 550

Example 49

7α-(9-Hydroxynonyl)-17α-methyl-3-oxoandrost-4-en-17ß-yl-acetate

13.9 g of the compound (23 mmol) that is produced under 44) is dissolved in 150 ml of methanol/tetrahydrofuran (2:1), 25 ml of 8% aqueous sulfuric acid is added, and it is stirred for 2 hours at room temperature. Then, it is diluted with ethyl acetate, washed out with saturated aqueous common salt solution, and the organic phase is concentrated by evaporation with sodium sulfate after drying. The residue is chromatographed on silica gel with dichloromethane/hexane, and the yield is 10.8 g (96% of theory) of the title compound.

Example 50

7α-(9-Chlorononyl)-17α-methyl-3-oxoandrost-4-en-17ß-yl-acetate

10.8 g of the compound that is produced under 49) is dissolved in 100 ml of tetrachloromethane and 35 ml of acetonitrile and reacted with 10.5 g of triphenylphosphine (40 mmol) at room temperature for 1 hour. Then, it is diluted with dichloromethane, shaken out with saturated aqueous sodium

bicarbonate and common salt solution, and the organic phase is dried wtih sodium sulfate and concentrated by evaporation. The oily residue is chromatographed on silica gel with hexane/^{t}butyl methyl ether, yield 10.2 g (91% of theory) of the title compound.

The following compounds were obtained analogously:

Ex.	Product Reagent (Precursor/Process)	Form	Yield [%]	MS	
				Cld.	Fnd.
51	7α-(9-Chlorononyl)-17ß-hydroxy-17α-methyl-androst-4-en-3-one Potassium carbonate/methanol (50\1c)	Oil	54	462 464	462 464
52	17ß-Hydroxy-7α-(9-iodononyl)-17α-methylandrost-4-en-3-one Sodium iodide (51\2)	Oil	80	554	554
53	17ß-Hydroxy-7α-(9-hydroxynonyl)-17α-methylandrost-4-en-3-one Potassium carbonate/methanol (49\1c)	Foam	74	444	444

54	7α-(7-Hydroxyheptyl)-17α-methyl-3-oxoandrost-4-en-17ß-yl-acetate Sulfuric acid (45\49)	Oil	98	458	458
55	17ß-Hydroxy-7α-(7-hydroxyheptyl)-17α-methylandrost-4-en-3-one Potassium carbonate/methanol (54\1c)	Foam	53	416	416
56	7α-(7-Chloroheptyl)-17ß-hydroxy-17α-methyl-androst-4-en-3-one Tetrachloromethane/tri-phenylphosphine (55\50)	Oil	80	434 436	434 436
57	17ß-Hydroxy-7α-(7-iodoheptyl)-17α-methylandrost-4-en-3-one Sodium iodide (56\2)	Flash Point 116°C	87	526	526
58	7α-(7-Bromoheptyl)-17ß-hydroxy-17α-methyl-androst-4-en-3-one Tetrabromomethane/tri-phenylphosphine (55/50)	Oil	55	479 481	479 481

59	7α-(10-Hydroxydecyl)-17α-methyl-3-oxoandrost-4-en-17ß-yl-acetate Sulfuric acid (46\49)	Oil	95	500	500
60	17ß-Hydroxy-7α-(10-hydroxydecyl)-17α-methylandrost-4-en-3-one Potassium carbonate/methanol (59\1c)	Oil	96	458	458
61	7α-(10-Chlorodecyl)-17ß-hydroxy-17α-methyl-androst-4-en-3-one Tetrachloromethane/tri-phenylphosphine (60\50)	Oil	24	476 478	476 478
62	7α-(11-Hydroxyundecyl)-17α-methyl-3-oxoandrost-4-en-17ß-yl-acetate Sulfuric acid (47\49)	Oil	95	514	514
63	17ß-Hydroxy-7α-(11-hydroxyundecyl)-17α-methylandrost-4-en-3-one Potassium carbonate/methanol (62\1c)	Oil	49	472	472

64	7α-(11-Bromoundecyl)-17ß-hydroxy-17α-methylandrost-4-en-3-one Tetrabromomethane/triphenylphosphine (63\50)	Oil	86	535 537	535 537
65	7α-[7-(4-Chlorobutoxy)heptyl]-17ß-hydroxy-17α-methylandrost-4-en-3-one Potassium carbonate/methanol (48\1c)	Oil	78	506 508	506 508
66	17ß-Hydroxy-7α-[7-(4-iodobutoxy)heptyl]-17α-methylandrost-4-en-3-one Sodium iodide (65\2)	Oil	92	598	598
67	17ß-Hydroxy-17α-methyl-7α-[7-(phenylsulfanyl)-heptyl]androst-4-en-3-one Sodium phenyl thiolate (57\4)	Oil	74	508	508
68	17ß-Hydroxy-17α-methyl-3-oxoandrost-4-ene-7α-decane nitrile Potassium cyanide (52\3)	Oil	44	453	453

Example 69

17ß-Hydroxy-17α-methyl-7α-[9-[(4,4,5,5,5-pentafluoropentyl)sulfanyl]nonyl]androst-4-en-3-one

0.07 ml of a 30% solution of sodium methanolate in methanol (0.33 mmol) is added to a solution of 69 mg of thioacetic acid-S-(4,4,5,5,5-pentafluoropentyl)ester (0.3 mmol), whose production is described in Li et al., **Tetrahedron Lett. 35**, 9141-9144 (1994), in 0.7 ml of methanol, and it is stirred for 30 minutes at room temperature. Then, a solution of 128 mg of the compound (0.23 mmol), produced under 52), in 2.3 ml of N,N-dimethylformamide is added. The reaction mixture is stirred overnight at room temperature, mixed with water and extracted three times with ethyl acetate. The organic phase is washed in succession with water and saturated aqueous sodium chloride solution, dried on sodium sulfate, filtered and concentrated by evaporation in a vacuum. The residue is chromatographed on silica gel with ethyl acetate/hexane, and the yield is 95 mg (66% of theory) of the title compound. MS: Cld. 620, Fnd. 620.

The following compounds were obtained analogously:

Ex.	Product Reagent (Precursor/Process)	Form	Yield [%]	MS	
				Cld.	Fnd.
70	7α-[9-(Acetylsulfanyl)nonyl]-17ß-hydroxy-17α-methylandrost-4-en-3-one Potassium thioacetate (52\3)	Oil	99	502	502
71	17ß-Hydroxy-17α-methyl-7α-[9-(pentylsulfanyl)nonyl]androst-4-en-3-one 1-Iodopentane (70\69)	Oil	32	530	530
72	17ß-Hydroxy-17α-methyl-7α-[9-(phenylsulfanyl)nonyl]androst-4-en-3-one Sodium phenyl thiolate (52\4)	Oil	62	536	536
73	5-[[9-(17ß-Hydroxy-17α-methyl-3-oxoandrost-4-en-7α-yl)nonyl]sulfanyl]pentanoic acid-methyl-ester 5-Iodopentanoic acid-methyl ester (70\69)	Oil	39	574	574

74	7α-[9-[(5-Chloropentyl)-sulfanyl]nonyl]-17ß-hydroxy-17α-methylandrost-4-en-3-one 1-Chloro-5-iodopentane (70\69)	Oil	42	564 566	564 566
75	5-[[9-(17ß-Hydroxy-17α-methyl-3-oxoandrost-4-en-7α-yl)nonyl]sulfanyl]pentane-nitrile 5-Bromopentanenitrile (70\69)	Oil	36	541	541
76a	7α-[9-[[5-[[(1,1-Dimethylethyl)dimethyl-silyl]oxy]pentyl]sulfanyl]-nonyl]-17ß-hydroxy-17α-methylandrost-4-en-3-one [(5-Bromopentyl)oxy](1,1-dimethylethyl)dimethylsilane (70\69)	Oil	98	661	661
76b	17ß-Hydroxy-7α-[9-[(5-hydroxypentyl)sulfanyl]nonyl]-17α-methylandrost-4-en-3-one Sulfuric acid (76a\49)	Oil	32	546	546

77	7α-[9-[(5-Bromopentyl)-sulfanyl]nonyl]-17ß-hydroxy-17α-methylandrost-4-en-3-one Tetrabromomethane/triphenyl-phosphine (76b\50)	Oil	28	609 611	609 611
78	7α-(9-Azidononyl)-17ß-hydroxy-17α-methyl-androst-4-en-3-one Sodium azide (52\3)	Oil	66	469	469
79	7α-[9-(Butylmethyl-amino)nonyl]-17ß-hydroxy-17α-methylandrost-4-en-3-one Butylmethylazan/bis(1-methylethyl)ethylazan (52\3)	Oil	35	513	513
80	7α-[7-(Acetylsulfanyl)heptyl]-17ß-hydroxy-17α-methylandrost-4-en-3-one Potassium thioacetate (57\3)	Oil	80	474	474
81	17ß-Hydroxy-17α-methyl-7α-[7-[(4,4,5,5,5-pentafluoropentyl)sulfanyl]-heptyl]androst-4-en-3-one Thioacetic acid-S-(4,4,5,5,5-pentafluoropentyl)ester (57\69)	Oil	84	592	592

82	7α-[7-(Butylmethyl-amino)heptyl]-17ß-hydroxy-17α-methylandrost-4-en-3-one Butylmethylazan/bis(1-methylethyl)ethylazan (57\3)	Oil	32	485	485
83	N-[7-(17ß-Hydroxy-17α-methyl-3-oxoandrost-4-en-7α-yl)heptyl]pentanamide Pentanamide (57\6)	Oil	18	499	499
84	17ß-Hydroxy-17α-methyl-3-oxoandrost-4-en-7α-octane-nitrile Potassium cyanide (57\3)	Oil	56	425	425
85	7α-(7-Azidoheptyl)-17ß-hydroxy-17α-methyl-androst-4-en-3-one Sodium azide (57\3)	Oil	77	441	441
86	N-[7-(17ß-Hydroxy-17α-methyl-3-oxoandrost-4-en-7α-yl)heptyl]methanesulfonamide Methanesulfonamide (57\6)	Oil	63	493	493

87	5-[[7-(17ß-Hydroxy-17α-methyl-3-oxoandrost-4-en-7α-yl)heptyl]oxy]pentanenitrile Potassium cyanide (66\3)	Oil	80	497	497
88	17ß-Hydroxy-7α-[7-(4-methoxybutoxy)heptyl]-17α-methylandrost-4-en-3-one Sodium methanolate/methanol (66\4)	Oil	48	502	502
89	7α-[7-[(But-3-enyl)oxy]heptyl]-17ß-hydroxy-17α-methylandrost-4-en-3-one Sodium methanolate/methanol (66\4)	Oil	14	470	470
90	17ß-Hydroxy-17α-methyl-7α-[11-[(4,4,5,5,5-pentafluoro-pentyl)sulfanyl]undecyl]androst-4-en-3-one Thioacetic acid-S-(4,4,5,5,5-pentafluoropentyl)ester (64\69)	Oil	62	648	648
91	17ß-Hydroxy-17α-methyl-7α-[11-(phenylsulfanyl)undecyl]-androst-4-en-3-one Sodium phenyl thiolate (64\4)	Oil	75	564	564

92	17ß-Hydroxy-7α-(11-methoxyundecyl)-17α-methylandrost-4-en-3-one Sodium methanolate/methanol (64/4)	Oil	57	486	486

Example 93

17ß-Hydroxy-17α-methyl-7α-[9-[(4,4,5,5,5-pentafluoropentyl)sulfinyl]nonyl]androst-4-en-3-one

83 mg of the compound that is produced under 69) is dissolved in 5 ml of dichloromethane, cooled in an ice bath, and 32 mg of 70% 3-chloroperbenzoic acid is added. After 15 minutes of stirring, it is mixed with saturated aqueous sodium thiosulfate solution, stirred for another 15 minutes and then diluted with dichloromethane. The organic phase is washed with saturated aqueous sodium bicarbonate solution and common salt solution, dried with sodium sulfate and concentrated by evaporation. The residue is chromatographed on silica gel on a thin-layer plate with acetone/hexane, and the yield is 52 mg (62% of theory) of the title compound. MS: Cld. 636, Fnd. 636.

The following compounds were obtained analogously:

Ex.	Product Reagent (Precursor\Process)	Form	Yield [%]	MS	
				Cld.	Fnd.
94	17ß-Hydroxy-17α-methyl-7α-[7-[(4,4,5,5,5-pentafluoro-pentyl)sulfinyl]heptyl]androst-4-en-3-one 3-Chloroperbenzoic acid (81\93)	Oil	65	608	608
95	17ß-Hydroxy-17α-methyl-7α-[7-[(4,4,5,5,5-pentafluoro-pentyl)sulfonyl]heptyl]androst-4-en-3-one 3-Chloroperbenzoic acid (81\93)	Oil	7	624	624
96	17ß-Hydroxy-17α-methyl-7α-[11-[(4,4,5,5,5-pentafluoro-pentyl)sulfinyl]undecyl]androst-4-en-3-one 3-Chloroperbenzoic acid (90\93)	Oil	66	664	664
97	17ß-Hydroxy-17α-methyl-7α-[11-[(4,4,5,5,5-pentafluoropentyl)sulfonyl]-undecyl]androst-4-en-3-one 3-Chloroperbenzoic acid (90\93)	Oil	12	680	680

98	17ß-Hydroxy-17α-methyl-7α-[7-(phenylsulfinyl)heptyl]androst-4-en-3-one 3-Chloroperbenzoic acid (67\93)	Oil	57	524	524
99	17ß-Hydroxy-17α-methyl-7α-[7-(phenylsulfonyl)heptyl]androst-4-en-3-one 3-Chloroperbenzoic acid (67\93)	Oil	26	540	540
100	17ß-Hydroxy-17α-methyl-7α-(9-sulfanylnonyl)androst-4-en-3-one Potassium carbonate/methanol (70\1c)	Oil	43	460	460

Example 101

17ß-Hydroxy-17α-methyl-3-oxoandrost-4-ene-7α-heptanoic acid

416 mg of the compound (1 mmol) that is produced under 55) is dissolved in 10 ml of anhydrous acetone and mixed with 5 ml of a 1 molar solution of Jones reagent (chromate solution) while being cooled with ice. After 15 minutes, it is mixed with saturated aqueous sodium sulfite solution, the acid solution is shaken out with ethyl acetate, the organic phase is extracted with saturated aqueous common salt solution, dried with sodium sulfate and concentrated by evaporation. The residue is chromatographed on silica gel with acetone/hexane, and the yield

is 78 mg (18% of theory) of the title compound. MS: Cld. 430, Fnd. 430.

Example 102

N-Butyl-17ß-hydroxy-N,17α-dimethyl-3-oxoandrost-4-ene-7α-heptanamide

78 mg of the compound that is produced under 101) is dissolved in 6 ml of dichloromethane, cooled to -10°C and mixed in succession with 30 µl of 4-methylmorpholine, 30 µl of chloroformic acid-(2-methylpropyl)ester and after 10 minutes with 40 µl of butylmethylazan. After 1 hour of stirring at room temperature, it is diluted with dichloromethane, extracted in succession with 1 molar aqueous sulfuric acid, saturated aqueous sodium bicarbonate solution and saturated common salt solution, the organic phase is dried with sodium sulfate and concentrated by evaporation. The residue is chromatographed on silica gel with acetone/hexane, and the yield is 40 mg (45% of theory) of the title compound. MS: Cld. 499, Fnd. 499.

The following compounds were obtained analogously:

Ex.	Product Reagent (Precursor\Process)	Form	Yield [%]	MS	
				Cld.	Fnd.
103	17ß-(Acetyloxy)-17α-methyl-3-oxoandrost-4-ene-7α-nonanoic acid Jones reagent (49\101)	Oil	13	500	500
104	17ß-(Acetyloxy)-N-butyl-N,17α-dimethyl-3-oxoandrost-4-ene-7α-nonanamide 4-Methylmorpholine/chloroformic acid-(2-methylpropyl)ester/butyl-methylazan (103\102)	Oil	90	569	569
105	N-Butyl-17ß-hydroxy-N,17α-dimethyl-3-oxo-androst-4-ene-7α-nonanamide Potassium carbonate/methanol (104\1c)	Oil	22	527	527
106	17ß-(Acetyloxy)-17α-methyl-3-oxoandrost-4-ene-7α-undecanoic acid Jones reagent (62\101)	Oil	15	528	528

107	17ß-(Acetyloxy)-N-butyl-N,17α-dimethyl-3-oxoandrost-4-ene-7α-undecanamide 4-methylmorpholine/ chloroformic acid-(2-methylpropyl)ester/butyl-methylazan (106\102)	Oil	86	597	597
108	N-Butyl-17ß-hydroxy-N,17α-dimethyl-3-oxo-androst-4-ene-7α-undecanamide Potassium carbonate/methanol (107\1c)	Oil	35	555	555

Example 109

2-[9-(17ß-Hydroxy-17α-methyl-3-oxoandrost-4-en-7α-yl)nonyl]propanedioic acid-diethyl ester

109a) 7α-(9-Chlorononyl)-3,3-[1,2-ethanediylbis(oxy)]-17α-methylandrost-4-en-17ß-ol

1.48 g of the compound that is produced under 51) is dissolved in 20 ml of dichloromethane, and 20 ml of 1,2-ethanediol, 12 ml of trimethoxymethane and 0.6 g of pyridinium-p-toluenesulfonate are added. The mixture is stirred overnight at room temperature, then mixed wtih triethylazan, diluted with dichloromethane and shaken out with water and saturated aqueous common salt solution. The organic phase is dried with sodium sulfate, concentrated by evaporation and chromatographed on silica gel with hexane/^{t}butyl methyl ether. The yield is 1.12 g

(69% of theory) of the title compound. MS: Cld. 506/508; Fnd. 506/508.

109b) 3,3-[1,2-Ethanediylbis(oxy)]-7α-(9-iodononyl)-17α-methylandrost-4-en-17ß-ol

1.09 g of the compound that is produced under 109a) is reacted analogously to the process that is described in Example 2) with 1.5 g of sodium iodide to form 1.37 g of the title compound as a colorless oil. MS: Cld. 598, Fnd. 598

109c) 2-[9-(17ß-Hydroxy-17α-methyl-3-oxoandrost-4-en-7α-yl)nonyl]propanedioic acid-diethyl ester

80 mg of propanedioic acid-diethyl ester in 0.5 ml of anhydrous tetrahydrofuran is deprotonated with 12 mg of 80% sodium hydride, 60 mg of the compound (0.1 mmol), produced under 109b), in 1 ml of anhydrous N,N-dimethylformamide is added, and it is heated for 5 hours to 80°C. After cooling, it is worked up as usual with ethyl acetate. The residue is dissolved in 0.5 ml of acetone and stirred with 0.1 ml of 4 molar aqueous hydrochloric acid for 15 minutes at room temperature. Then, it is worked up with ethyl acetate again and chromatographed. The yield is 29 mg (49% of theory) of the title compound. MS: Cld. 586, Fnd. 586.

The following compounds were obtained analogously:

Ex.	Product Reagent (Precursor\Process)	Form	Yield [%]	MS	
				Cld.	Fnd.
110	2-[2-Acetyl-9-(17ß-hydroxy-17α-methyl-3-oxoandrost-4-en-7α-yl)nonyl]undecanoic acid ethyl ester 3-Oxobutanoic acid ethyl ester (109b\109c)	Oil	51	556	556
111	17ß-Hydroxy-17α-methyl-7α-[9-(pentyloxy)nonyl]androst-4-en-3-one 1-Pentanol (109b\109c)	Oil	23	514	514
112	N-[9-(17ß-Hydroxy-17α-methyl-3-oxoandrost-4-en-7α-yl]nonyl]pentanamide Pentanamide (109b\109c)	Oil	21	527	527
113	N-[9-(17ß-Hydroxy-17α-methyl-3-oxoandrost-4-en-7α-yl)nonyl]methanesulfonamide Methanesulfonamide (109b\109c)	Oil	57	521	521

Example 114

7α-(9-Chlorononyl)-6ß-hydroxy-17α-methyl-3-oxoandrost-4-en-17ß-yl-acetate

3.3 g of the compound that is produced under 50) is dissolved in 22 ml of 2,2-dimethoxypropane, 0.4 g of pyridinium-p-toluenesulfonate is added, and it is refluxed for 22 hours. After the cooling, it is mixed with triethylazan and evaporated to the dry state. The residue is chromatographed on silica gel with hexane/^{t}butyl methyl ether. 2.91 g of 7α-(9-chlorononyl)-3-methoxy-17α-methylandrosta-3,5-dien-17ß-yl-acetate-(84% of theory) is obtained and is immediately further reacted.

This substance is suspended in 60 ml of a mixture of ethanol/water 95:5, mixed with 1.7 g of 3-chloroperbenzoic acid (6.8 mmol) and stirred for 45 minutes at room temperature. Then, 5 ml of 2 molar aqueous sulfuric acid is added, stirred for 15 minutes at room temperature and diluted with ethyl acetate. The organic phase is shaken out with water and saturated aqueous solutions of sodium dithionate, sodium bicarbonate and common salt, dried with sodium sulfate and concentrated by evaporation. After chromatography on silica gel with hexane/ethyl acetate, 1.0 g (30% of theory) of the title compound is obtained. MS: Cld. 520/522, Fnd. 520/522.

The following compounds were obtained analogously:

Ex.	Product Reagent (Precursor\Process)	Form	Yield [%]	MS	
				Cld.	Fnd.
115	6ß-Hydroxy-7α-(9-hydroxynonyl)-17α-methyl-3-oxoandrost-4-en-17ß-yl-acetate 3-Chloroperbenzoic acid (49\114)	Oil	8	502	502
116	6ß,17ß-Dihydroxy-7α-(7-hydroxyheptyl)-17α-methylandrost-4-en-3-one 3-Chloroperbenzoic acid (55\114)	Oil	9	432	432
117	6ß,17ß-Dihydroxy-17α-methyl-3-oxoandrost-4-en-7α-octane-nitrile 3-Chloroperbenzoic acid (84\114)	Oil	8	441	441
118	7α-[7-(4-Chlorobutoxy)heptyl]-6ß,17ß-dihydroxy-17α-methylandrost-4-en-3-one 3-Chloroperbenzoic acid (65\114)	Oil	14	522 524	522 524

Example 119: Antiproliferation Test with the Human Prostate Cancer Cell Line (LNCaP)

The human prostate cancer cell line LNCaP [American Type Culture Collection (ATCC) = Accession No.: CRL 1740; Horoszewicz et al., **Cancer Research, 43**, pp. 1809-18, 1983] was isolated from the lymph node metastasis of a prostate cancer patient. It expresses the androgen receptor and can be stimulated in growth by androgens. The androgen-mediated growth stimulation can be blocked by simultaneous administration of antiandrogens. The antiandrogenic active strength (IC50) of test compounds can be determined by dose-action correlations. If a single administration of a test compound leads to growth stimulation, this can be explained by an androgenic action which the compounds according to the invention are not to exhibit.

Execution:

The cells are cultivated in RPMI 1640 medium with penicillin (10,000 units/l), streptomycin (100 mg/l), glutamine (200 mmol), 10% fetal calf serum and 0.1 nM of the synthetic androgen R1881 (Metribolone, Roussel).

Day 1: Sowing of the cells in a density of 5,000-6,000/100 µl/hole in 96-hole plates. Adding test compound (100 µl/hole doubly concentrated) to the culture medium with 0.2 nM of R1881 (yields 0.1 nM final concentration). Incubation of the cells for 72 or 96 hours at 37°C, 5% CO_2, 90% relative atmospheric humidity. In the culture medium, the fetal calf serum is replaced by 5% activated carbon-treated (steroid-free) serum.

Day 3 or 4: Medium change: In each case in 50% of the medium, inclusive test compounds are replaced by fresh medium. Incubation of the cells for 96 or 72 hours at 37°C, 5% CO2, 90% relative atmospheric humity.

Day 7: Adding 25 μl of MTT solution per hole {MTT = (3[4,5-dimethylthiazol-2-yl]-2,5-diphenaltetrazolium bromide (thiazolyl blue}. Incubation is for 3 hours at 37°C, 5% CO_2, 90% relative atmospheric humidity. After the removal of the supernatant, addition of 100 μl of DMSO per hole. Measurement of the optical density at 570 mm.

The antiandrogens OH-flutamide and casodex that are found in clinical practice were tested, as well as the compound EM-101 (N-butyl, N-methyl-11-(17'ß-hydroxy-4'-androsten-3'-on-7'α-yl)undecanamide of WO 91/00732.

Results:

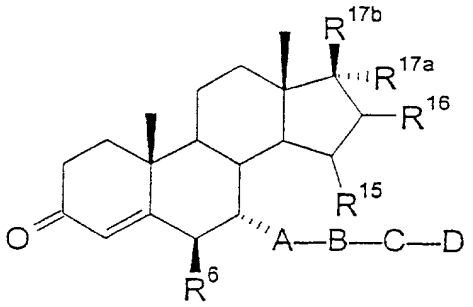
	Antiandrogeneity	Androgeneity
	IC50 in the presence of 0.1 nM of R1881	at 1 μM*
OH-flutamide	> 10,000 nM	144%
Casodex	440 nM	7%
EM-101	4440 nM	0%
Example 53	40 nM	0%
Example 80	200 nM	0%
Example 87	82 nM	0%

*The growth stimulation by 0.1 nM of R1881 was set = 100%.

The results show that the compounds according to the invention exert no androgenic action in the case of an improved antiandrogenic action (lower IC_{50} values).

Claims

1. Testosterone derivatives of general formula I



(I)

in which

R^6 represents a hydrogen atom, a hydroxy group, a C_1-C_{10} alkoxy group, a C_1-C_{10} alkanoyloxy group or a halogen atom,

R^{15} and R^{16} each are a hydrogen atom or together form a bond,

R^{17a} represents a C_1-C_4 alkyl group, a C_2-C_4 alkinyl group, or a radical of Formula $C_nF_mH_o$, whereby n = 1, 2, 3 or 4, m > 1 and m+o=2n+1,

R^{17b} is a hydroxy group, a C_1-C_{10} alkoxy group or a C_1-C_{10} alkanoyloxy group,

A is an unbranched C_6-C_{13} alkylene group,

B represents an oxygen atom, a grouping $-S(O)_p$, whereby p = 0, 1 or 2, an iminocarbonyl group -C(O)N(Y)-, an imino group -N(Y)-, a carbonylimino group -N(Y)C(O)-, a sulfonylimino group $-N(Y)S(O)_2-$, whereby Y is a hydrogen atom or a C_1-C_8 alkyl group, a sulfonyloxy group $-OS(O)_2-$, a dimethylsilyloxy group $-O-Si(CH_3)_2-$ or

a carbonylsulfanyl group -SC(O)-, or B represents a bond between A and C or together with C forms a bond between A and D,

C represents a bond between B and D, or together with B forms a bond between A and D or an unbranched C_1-C_6 alkylene group, a phenylene group, a substituted phenylene group, a five-ring or six-ring heteroarylene group, a substituted five-ring or six-ring heteroarylene group or a five-ring or six-ring heteroarylene group that is condensed with a phenyl ring,

and

D represents a hydrogen atom, a C_1-C_4 alkyl group, a vinyl group, a C_1-C_4 alkoxy group, a C_1-C_4 alkoxycarbonyl group, a bis(C_1-C_4 alkoxycarbonyl)methyl group, an acetyl(C_1-C_4 alkoxycarbonyl)methyl group, a cyano group, a carboxy group, an azide group, a hydroxy group, a halogen atom or a radical of formula $C_nF_mH_o$, whereby n = 1, 2, 3 or 4, m > 1 and m+o=2n+1.

2. Testosterone derivatives according to claim 1, characterized in that R^{17a} represents the methyl group, the ethyl group, the trifluoromethyl group or the pentafluoroethyl group.

3. Testosterone derivatives according to claim 1 or 2, wherein R^{17b} is the hydroxy group, a C_1-C_5 alkoxy group or a C_1-C_3 alkanoyloxy group.

4. Testosterone derivatives according to claim 3, wherein R^{17b} is the hydroxy, methoxy, ethoxy or acetyloxy group.

5. Testosterone derivatives according to one of claims 1 to 4, wherein R^6 represents a hydrogen atom, the hydroxy group or a halogen atom.

6. Testosterone derivatives according to one of claims 1 to 5, wherein R^{15} and R^{16} each represent a hydrogen atom.

7. Testosterone derivatives according to one of claims 1 to 6, wherein radical ABCD means 9-hydroxynonyl, 7-(acetylsulfanyl)heptyl or 7-(4-cyanobutoxy)heptyl.

8. Testosterone derivatives according to one of claims 1 to 6, wherein the five-ring- or six-ring-heteroaromatic compounds of radical C are pyrrole, thiophene, imidazole, thiazole, oxazole, triazole, thiadiazole, indole, benzoxazole, benzothiazole, pyridine, or pyrimidine.

9. Testosterone derivatives according to one of claims 1 to 8, wherein they represent the following compounds:

7α-(9-Chlorononyl)-17α-methyl-3-oxoandrost-4-en-17ß-yl-acetate

7α-(9-Chlorononyl)-17ß-hydroxy-17α-methylandrost-4-en-3-one

17ß-Hydroxy-7α-(9-iodononyl)-17α-methylandrost-4-en-3-one

17ß-Hydroxy-7α-(9-hydroxynonyl)-17α-methylandrost-4-en-3-one

7α-(10-Chlorodecyl)-17ß-hydroxy-17α-methylandrost-4-en-3-one

17ß-Hydroxy-7α-(11-hydroxyundecyl)-17α-methylandrost-4-en-3-one

7α-(11-Bromoundecyl)-17ß-hydroxy-17α-methylandrost-4-en-3-one

17ß-Hydroxy-17α-methyl-7α-[7-(phenylsulfanyl)heptyl]androst-4-en-3-one

17ß-Hydroxy-17α-methyl-7α-[9-[(4,4,5,5,5-pentafluoropentyl)sulfanyl]nonyl]androst-4-en-3-one

17ß-Hydroxy-17α-methyl-7α-[9-(phenylsulfanyl)nonyl]androst-4-en-3-one

7α-[9-[(5-Chloropentyl)sulfanyl]nonyl]-17ß-hydroxy-17α-methylandrost-4-en-3-one

17ß-Hydroxy-7α-[9-[(5-hydroxypentyl)sulfanyl]nonyl]-17α-methylandrost-4-en-3-one

7α-(9-Azidononyl)-17ß-hydroxy-17α-methylandrost-4-en-3-one

7α-[7-(Acetylsulfanyl)heptyl]-17ß-hydroxy-17α-methylandrost-4-en-3-one

17ß-Hydroxy-17α-methyl-7α-[7-[(4,4,5,5,5-pentafluoropentyl)sulfanyl]heptyl]androst-4-en-3-one

N-[7-(17ß-Hydroxy-17α-methyl-3-oxoandrost-4-en-7α-yl)heptyl]pentanamide

17ß-Hydroxy-17α-methyl-3-oxoandrost-4-en-7α-octane nitrile

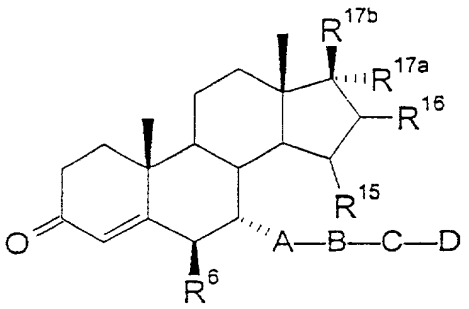
5-[[7-(17ß-Hydroxy-17α-methyl-3-oxoandrost-4-en-7α-yl)heptyl]oxy]pentanenitrile

17ß-Hydroxy-17α-methyl-7α-[9-[(4,4,5,5,5-pentafluoropentyl)sulfinyl]nonyl]androst-4-en-3-one

N-[9-(17ß-Hydroxy-17α-methyl-3-oxoandrost-4-en-7α-yl)nonyl]methanesulfonamide

7α-(9-Chlorononyl)-6ß-hydroxy-17α-methyl-3-oxoandrost-4-en-17ß-yl-acetate

10. Use of the testosterone derivatives of general formula I



(I)

in which

R^6 represents a hydrogen atom, a hydroxy group, a C_1-C_{10} alkoxy group, a C_1-C_{10} alkanoyloxy group or a halogen atom,

R^{15} and R^{16} each are a hydrogen atom or together form a bond,

R^{17a} represents a C_1-C_4 alkyl group, a C_2-C_4 alkinyl group, or a radical of Formula $C_nF_mH_o$, whereby n = 1, 2, 3 or 4, m > 1 and m+o=2n+1,

R^{17b} is a hydroxy group, a C_1-C_{10} alkoxy group or a C_1-C_{10} alkanoyloxy group,

A is an unbranched C_6-C_{13} alkylene group,

B represents an oxygen atom, a grouping $-S(O)_p$, whereby p = 0, 1 or 2, an iminocarbonyl group -C(O)N(Y)-, an imino group -N(Y)-, a carbonylimino group -N(Y)C(O)-, a sulfonylimino group $-N(Y)S(O)_2-$, whereby Y is a hydrogen atom or a C_1-C_8 alkyl group, a sulfonyloxy group $-OS(O)_2-$, a dimethylsilyloxy group $-O-Si(CH_3)_2-$ or a carbonylsulfanyl group -SC(O)-, or B represents a

bond between A and C or together with C forms a bond between A and D,

C represents a bond between B and D, or together with B forms a bond between A and D or an unbranched C_1-C_6 alkylene group, a phenylene group, a substituted phenylene group, a five-ring or six-ring heteroarylene group, a substituted five-ring or six-ring heteroarylene group or a five-ring or six-ring heteroarylene group that is condensed with a phenyl ring,

and

D represents a hydrogen atom, a C_1-C_4 alkyl group, a vinyl group, a C_1-C_4 alkoxy group, a C_1-C_4 alkoxycarbonyl group, a bis(C_1-C_4 alkoxycarbonyl)methyl group, an acetyl(C_1-C_4 alkoxycarbonyl)methyl group, a cyano group, a carboxy group, an azide group, a hydroxy group, a halogen atom or a radical of formula $C_nF_mH_o$, whereby n = 1, 2, 3 or 4, m > 1 and m+o=2n+1

for long-term antiandrogen therapy for androgen-dependent diseases.

11. Use according to claim 10, wherein the testosterone derivatives are used for long-term therapy for prostate cancer.

12. Use according to claim 10 or 11, wherein the testosterone derivatives that are described in more detail in Claims 2 to 9 are used.

13. Pharmaceutical agents that contain at least one testosterone derivative of general formula I according to claims

1 to 9 and physiologically compatible adjuvants and/or vehicles that are commonly used in galenicals.

DECLARATION FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

NEW 7-ALPHA, 17-ALPHA-BIS-ALKYLATED TESTOSTERONE DERIVATIVES AND THEIR USE IN LONG-TERM THERAPY OF ANDROGEN-DEPENDENT DISEASES

the specification of which

☐ is attached hereto

was filed on 23 DECEMBER 1999 as United States Application Number or PCT International Application Number PCT/EP99/10355 and (if applicable) was amended on _____

I hereby authorize our attorneys to insert the serial number assigned to this application

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1 56.

I hereby claim foreign priority benefits under 35 U.S.C §119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 USC §119			
APPLICATION NO.	COUNTRY	DAY/MONTH/YEAR FILED	PRIORITY CLAIMED
198 60 719.9	GERMANY	23 DECEMBER 1998	

I hereby claim the benefit under 35 U S.C. §119(e) of any United States provisional application(s) listed below.

PROVISIONAL APPLICATION(S) UNDER 35 U.S.C. §119(e)	
APPLICATION NUMBER	FILING DATE

I hereby claim the benefit under 35 U.S.C. §120 of any United States application, or §365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. §112.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1 56 which became available between the filing date of the prior application and the national or PCT International filing date of this application

PRIOR U.S./PCT INTERNATIONAL APPLICATION(S) DESIGNATED FOR BENEFIT UNDER 37 U.S.C. §120		
APPLICATION NO.	FILING DATE	STATUS — PATENTED, PENDING, ABANDONED

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected herewith: I. William Millen (19,544); John L. White (17,746); Anthony J. Zelano (27,969), Alan E.J. Branigan (20,565); John R. Moses (24,983); Harry B. Shubin (32,004); Brion P. Heaney (32,542); Richard J. Traverso (30,595); John A. Sopp (33,103); Richard M. Lebovitz (37,067), John H. Thomas (33,460); Catherine M. Joyce (40,668); Nancy J. Axelrod (44,014), James T. Moore (35,619); James E. Ruland (37,432); Jennifer J. Branigan (40,921) and Robert E McCarthy (46,044)

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PATENT TRADEMARK OFFICE

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the specification of which

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon

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☐ Additional joint inventors are named on separately numbered sheets attached hereto

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon

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☐ Additional joint inventors are named on separately numbered sheets attached hereto